SUMMARY OF CHANGES

For Protocol Amendment #7 to #8

UPCI #: 13-182

Protocol Date: 05/02/17

#	Section	Page(s)	Change
1.	Title page	1	Update protocol version and version date.
2.	Header	All	Update protocol version date.
3.	BIOMARKER ASSESSMENTS	5	Information is added for optional research biopsies at the time of progression.
4.	LIST OF ABBREVIATIONS	8-9	Added FNA for *Fine needle aspirate*, and IHC for *Immunohistochemical*.
5.	3.2 Exclusion Criteria	27	Exclusion criterion 2 is revised to reduce the exposure interval of prior treatment with a small molecule kinase inhibitor or hormonal therapy, from 14 days to 7 days. The interval is shortened in order to lower the risk of pseudo-progression that can occur in patients with oncogene driven disease upon withdrawal of targeted therapy.
6.	9. BIOMARKER STUDIES	60	Information is added for optional research biopsies at the time of progression.
7.	10. STUDY CALENDAR	62-3	Added the Optional Tumor Tissue Biopsy at disease progression, and associated footnote 14 including information that subject must provide consent to undergo the tissue biopsy.

UPMC CancerCenter

Partner with University of Pittsburgh Cancer Institute

TITLE: A SINGLE-ARM PHASE II CLINICAL TRIAL OF CABOZANTINIB (XL184) IN PATIENTS WITH PREVIOUSLY TREATED NON-SMALL CELL LUNG CANCER (NSCLC) WITH BRAIN METASTASES WITH AND WITHOUT *C-MET* AMPLIFICATION

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SYNOPSIS

RATIONALE

Seventeen to thirty percent of patients with newly diagnosed NSCLC will present with metastatic disease to the brain.[1-3] Treatment options for brain metastases from NSCLC include whole–brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), surgical resection or some combination of these options. The median survival time after whole-brain radiation therapy usually ranges from 3-6 months and strongly correlates with the patient's age, performance status, number and location of metastatic lesions.[4-6] In addition, whole brain radiotherapy may cause devastating CNS damage. The majority of patients with brain metastases also suffer from active extracranial disease, and systemic disease progression is a common cause of death. Therefore, development of effective systemic treatment for control of both extracranial and brain metastases is desirable.

There are an increasing number of drug trials that are specifically focusing on patients with brain metastases. One of possibly targetable pathways is the HGF/MET pathway. The c-MET receptor tyrosine kinase has been implicated in tumor cell migration, invasion, proliferation and angiogenesis and is the only known high affinity receptor for hepatocyte growth factor (HGF).[7] Amplification of c-MET has been associated with poor prognosis in NSCLC, mediastinal lymph node metastases, and resistance, both acquired and intrinsic, to EGFR tyrosine kinase inhibitors in EGFR-mutant lung adenocarcinoma.[8-10] c-MET expression and phosphorylation has been shown to be associated with the development of NSCLC brain metastases and are selectively enriched in brain metastases relative to paired primary lung tumors.[11] Of most importance, the presence of de novo c-MET amplification in NSCLC has been linked to rapid and durable clinical response to single agent crizotinib, a c-MET receptor tyrosine kinase inhibitor. [12]

In a series of 200 NSCLC brain metastases collected at the University of Pittsburgh Medical Center (UPMC) between 2005 and 2012, 50% were of adenocarcinoma histology. To date we have completed FISH studies on 77 of these brain metastases. Twenty-one percent (16 of 77) of these brain metastases were c-MET amplified as defined by a FISH ratio > 2.0; 38% (6 of 16) of these c-MET amplified brain tumors also harbored a KRAS mutation (confidential unpublished data). These data are intriguing in its marked inconsistency with the ongoing genotyping efforts of the Lung Cancer Mutation Consortium (LCMC), in which c-MET amplification was present in only 5 (1%) of 733 metastatic lung adenocarcinomas that underwent profiling for 10 oncogenic drivers. Furthermore, 96% of the oncogenic drivers identified through the LCMC were mutually exclusive. These data suggest that c-MET amplification plays a critical role in the metastatic potential of NSCLC to the brain and implicates c-MET as a therapeutic target in NSCLC with brain metastases, in particular, the subset with c-MET amplification.

Cabozantinib (XL184) is a potent oral inhibitor of MET, VEGFR2, and RET that produces robust antiangiogenic and antitumor effects in preclinical models. The efficacy of single agent cabozantinib was evaluated in patients with progressive glioblastoma multiforme (GBM) in a phase II open-label clinical trial at 140 mg daily and 100 mg daily dose levels. Cabozantinib at both dose levels was associated with objective responses in central nervous system disease. The objective response rates (ORR) in patients who were naïve to prior treatment with anti-angiogenic therapy were 21% and 30%, at the 140 mg and 100 mg dose levels, respectively, suggesting blood-brain barrier penetration. In a randomized discontinuation study in molecularly unselected NSCLC patients, cabozantinib given

at 100 mg orally daily was associated with a 10% ORR and an overall disease control rate (DCR; partial response plus stable disease) of 38% at 12 weeks. This current trial is a single-arm phase II clinical trial evaluating the efficacy and safety of cabozantinib in NSCLC patients with brain metastases both in an unselected population and in a subset with c-MET amplification.

STUDY DESIGN

This is a single institution open-label phase II clinical trial designed to allow a preliminary assessment of the efficacy and safety of cabozantinib in unselected NSCLC patients with metastases to the brain and in the subset of patients with c-MET amplified NSCLC with metastases to the brain. Previously treated patients with non-squamous NSCLC who have had brain metastases at any point in their treatment history are eligible for enrollment on this clinical trial. Patients with clinically asymptomatic untreated brain metastases will be allowed on trial at the discretion of the treating investigator. Patients who have undergone treatment for their brain metastases with WBRT, SRS or surgery must be clinically stable and recovered from all procedures at the time of study enrollment. Patients will receive cabozantinib at 60 mg once daily and continue on treatment until disease progression, death or unacceptable adverse events.

A Simon's optimal two-stage design is used to minimize the expected sample size if the treatment is not effective. The target enrollment is 54 evaluable patients. Patients must have adequate tumor tissue available to complete c-MET FISH studies as well as routine molecular profiling at the UPMC. A minimum of 15 evaluable patients with c-MET amplified tumors, as determined by a FISH ratio (c-MET/CEP7) > 2.0 based on testing of the primary tumor and/or site of metastatic disease, will be required.

OBJECTIVES

Primary Objectives:

- To assess the ORR in patients with NSCLC and brain metastases treated with cabozantinib.
- To assess the ORR of cabozantinib in patients with c-MET amplified NSCLC and brain metastases

Secondary Objectives:

- To assess the DCR at 16 weeks, the progression-free survival (PFS), the overall survival (OS) and the safety and tolerability of cabozantinib in patients with NSCLC and brain metastases.
- To assess the DCR at 16 weeks, the PFS, the OS and the safety and tolerability of cabozantinib in patients with c-MET amplified NSCLC with brain metastases.
- To assess the time to progression (TTP) of intracranial disease with cabozantinib.

Exploratory Objectives:

- To perform correlative studies to identify potential biomarkers of response to cabozantinib, including other known oncogenic drivers in lung adenocarcinoma and HGF co-expression.

INVESTIGATIONAL REGIMEN DOSE/ ROUTE/ DURATION

Cabozantinib is supplied as 20, 60-mg tablets.

Patients will receive cabozantinib at 60 mg once daily and continue on treatment until disease progression, death or unacceptable adverse events. Treatment cycles are 4 weeks in duration.

TUMOR ASSESSMENTS

- Computed tomography scans every 8 weeks for assessment of extra-cranial disease will be performed.
- MRI of the brain with contrast (or CT brain with contrast in patients who are unable to obtain an MRI, e.g., has a pacemaker) every 8 weeks to assess intracranial disease will be performed.
    - In patients whose first site of disease progression is extra-cranial disease, a brain MRI (or CT brain with contrast in patients who are unable to obtain an MRI) will be performed at the time of extra-cranial disease progression and every 12 weeks in the study follow-up period.

SAFETY ASSESSMENTS

Safety will be monitored on an ongoing basis. Laboratory testing (chemistry, hematology tests) will be performed every 2 weeks for the first 12 weeks followed by assessments every 4 weeks. Other safety evaluations including EKGs and urine protein-creatinine ratio (UPCR) will be performed at regular intervals.

Adverse event seriousness, severity grade, and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

BIOMARKER ASSESSMENTS

Tumor tissue will be mandated at time of study enrollment. All tumors will undergo routine molecular testing (as part of the standard of care) at UPMC, which includes Sanger sequencing and SNaPshot analysis for the detection of mutations in the EGFR exons 18-21, KRAS codons 12, 13 and 61, BRAF codon 600 and PIK3CA codons 542, 545 and 1047, in addition to FISH for the EML4-ALK rearrangement, ROS1 rearrangement, c-MET amplification and the KIF5B-RET translocation. In patients who do not have an oncogenic driver on routine mutational profiling, the tumors will undergo next generation sequencing using the Ion AmpliSeq™ Cancer Panel on Ion Torrent PGM (Life Technologies) (also standard at UPMC).

Serum, plasma, and peripheral blood mononuclear cell (PBMC) samples will be collected at baseline (C1D1) as well on day 1 of cycles 2 and 3 and then at time of progression. We hypothesize that markers of increased HGF/MET dependence (MET amplification, MET mutation, high MET expression, high serum HGF and/or sc-MET) at baseline will predict response to cabozantinib and an increase in serum HGF and/or sc-MET after treatment may predict lack of response. We will analyze the predictive value high serum levels of HGF and sc-MET at baseline and during treatment. Baseline and serial HGF and sc-MET as well as other potential biomarker serum levels will be

measured using ELISA. Future genetic polymorphism testing planned on PBMCs if subject agrees.

c-MET expression (IHC) will also be determined utilizing the SP44 antibody and correlated with c-MET FISH. HGF expression has been shown to be a key predictor of response to c-MET inhibition in both glioblastoma cell lines and xenograft models.[13] HGF expression will be determined on tumors samples as a potential predictor of clinical response.

In addition to mandatory archival or tissue from new biopsy at baseline, we will obtain optional research biopsies at time of progression. These samples will allow us to identify both biomarkers for response as well as mechanisms of acquired resistance to cabozantinib. The tissue samples will be used for research purposes (immunohistochemical [IHC] biomarker studies) as well as standard CLIA-certified molecular testing. If a targetable alteration is identified then this may guide post-progression therapy. A core biopsy is preferable, fine needle aspirate (FNA) is acceptable, from the most accessible site at which disease progression is evident. In addition to the biomarker assessments listed above for baseline tumor tissue, we will also perform next generation sequencing using the Ion AmpliSeq™ Cancer Panel on Ion Torrent PGM (Life Technologies) (also standard at UPMC). This 50-gene cancer panel includes our standard clinical metastatic lung cancer panel (including *KRAS*, *PIK3CA*, *BRAF*, and *EGFR*) as well as additional genes of interest (*HRAS*, *AKT1*, *PTEN*, *STK11*, *JAK2/3* and *TP53*, and *CDKN2A*).

STATISTICAL METHODS

This phase II trial is designed to allow preliminary assessment of the efficacy and safety of cabozantinib in NSCLC patients with metastases to the brain and in the subset of patients with c-MET amplified NSCLC with metastases to the brain.

The hypothesis is that cabozantinib increases ORR from 5% to 15% in patients with NSCLC with brain metastases. The historical ORR in the second–line setting is based on a 5.8% response rate in patients with recurrent NSCLC treated with docetaxel.[14] In a prior study of patients with metastatic NSCLC, the 12-week ORR for cabozantinib was 10% (95% confidence interval 5%-20%).[8] Based on our preliminary data, we anticipate a higher ORR in patients with brain metastases.

Therefore, target enrollment is 54 evaluable patients. Simon's optimal two-stage design is used to minimize the expected sample size if the treatment is not effective. A stopping rule for futility is implemented if 1 or fewer of the first 29 evaluable patients have an objective response. (Accrual may continue during follow-up for these patients.) If ≥2 responses are observed in the first 29 evaluable patients, an additional 25 patients will be enrolled. A promising study result would be a response rate of 6/54 (11%) or greater. This design has 82% power to detect a true response rate of 15% (compared with a null rate of 5%). A minimum of 15 evaluable patients with c-MET amplified tumors will be enrolled. If 1 or fewer than 29 patients in the first stage of the Simon design have an objective response and fewer than 15 of the 29 have c-MET amplified tumors, accrual will continue for the c-MET amplified patients only to reach a minimum of 15 evaluable patients with c-MET amplification.

The ORR will be reported for the unselected population (all evaluable patients) and for patients with c-MET amplification. A 90% and 95% Wilson confidence interval for the ORR will also be reported. With a minimum of 15 patients with c-MET amplification a promising ORR should be detectable. For example, the 95% Wilson confidence interval for a 3/15 ORR (20%) is (7%, 45%).

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration time curve
$AUC_{0\text{-last}}$	AUC from time zero to the last quantifiable time point
$AUC_{0\text{-}\infty}$	AUC from time zero to infinity
BP	blood pressure
BUN	blood urea nitrogen
C_{max}	maximum plasma concentration
CPK	creatine phosphokinase
cPR	confirmed partial response
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRPC	castration-resistant prostate cancer
CSF	colony stimulating factor
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
DCR	disease control rate
DLT	dose limiting toxicity
DTC	differentiated thyroid cancer
DVT	deep vein thrombosis
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ED_{50}	dose required for 50% inhibition
ESC	Exelixis Safety Committee
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
FNA	Fine needle aspirate
FLT3	FMS-like tyrosine kinase 3
FSH	follicle-stimulating hormone
GABA	γ-aminobutyric acid
GB	glioblastoma
GCP	Good Clinical Practice
GI	gastrointestinal
GEJ	gastroesophageal junction
GnRH	gonadotropin-releasing hormone
HCC	hepatocellular carcinoma
HEENT	head eye ear nose and throat

HGF	hepatocyte growth factor
IC_{50}	concentration required for 50% inhibition
ICH	International Conference on Harmonisation
IHC	Immunohistochemical
IME	important medical event
INR	International Normalized Ratio
IRB	Institutional Review Board
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
LMWH	low molecular weight heparin
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small-cell lung cancer
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PBMC	Peripheral blood mononuclear cell
PD	progressive disease
PE	pulmonary embolism
PFS	progression-free survival
PFS6	progression-free survival at 6 months
P-gp	P-glycoprotein
PI	principal investigator
PIB	powder-in-bottle
PK	pharmacokinetic
PO	oral
PPE	palmar-plantar erythrodysesthesia
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
qd	once daily
QTc	corrected QT
QTcF	QTc calculated by the Fridericia formula
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	reversible posterior leukoencephalopathy syndrome
RTK	receptor tyrosine kinase

SAE	serious adverse event
SBP	systolic blood pressure
SD	stable disease
SCLC	small-cell lung cancer
$t_{1/2, z}$	terminal-phase half-life
t_{max}	time to the maximum plasma concentration
TFT	thyroid function test
TIA	transient ischemic attack
TSH	thyroid stimulating hormone
TTP	time to progression
ULN	upper limit of normal
UPCR	urine protein/urine creatinine ratio
VEGF(R)	vascular endothelial growth factor (receptor)

1. OBJECTIVES

1.1 Primary Objectives

- To assess the overall response rate (ORR) in patients with NSCLC and brain metastases treated with cabozantinib.
- To assess the ORR of cabozantinib in patients with c-MET amplified NSCLC and brain metastases

1.2 Secondary Objectives

- To assess the disease control rate (DCR) at 16 weeks, the progression-free survival (PFS), the overall survival (OS) and the safety and tolerability of cabozantinib in patients with NSCLC and brain metastases.
- To assess the DCR at 16 weeks, the PFS, the OS and the safety and tolerability of cabozantinib in patients with c-MET amplified NSCLC with brain metastases.
- To assess the time to progression (TTP) of intracranial disease with cabozantinib.

1.3 Exploratory Objectives

- To perform correlative studies to identify potential biomarkers of response to cabozantinib, including other known oncogenic drivers in lung adenocarcinoma and HGF co-expression

2. BACKGROUND

2.1 Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the leading cause of cancer mortality in the United States and worldwide.[15] An estimated 226,160 new cases of lung cancer will be diagnosed in 2012 in the United States alone, and 160,340 lung cancer deaths are estimated to occur. The five year survival for all lung cancer patients is a dismal 15%. Historically, non-small cell lung cancer (NSCLC) was treated as a single disease entity, and palliative chemotherapy in the metastatic setting resulted in modest survival prolongation and preservation of quality of life.[16-20] A series of large randomized controlled phase III clinical trials established platinum-based doublets as the standard of care in the treatment of metastatic NSCLC with response rates of 20-30% and a median survival of 8-11 months.[21-25]

Recent advances in the treatment of metastatic NSCLC have come from recognition that NSCLC is not a single disease entity, but rather a collection of distinct molecularly-driven neoplasms. Lynch *et al.* and Paez *et al.* first described a subset of patients with NSCLC harboring activating mutations in the *EGFR* gene who responded to treatment with EGFR tyrosine kinase inhibitors (TKIs).[26, 27] This discovery permanently shifted the landscape of NSCLC therapy to a personalized approach based on the molecular alterations of a patient's tumor; a paradigm typified not only by targeted therapies in *EGFR* mutant lung adenocarcinomas, but also in *ALK* translocation driven adenocarcinomas of the lung and more recently, the therapeutic advances in lung adenocarcinomas harboring *ROS1* gene rearrangements and *BRAF* mutations.[28-30]

The MET protein is a receptor tyrosine kinase receptor which upon binding its only known physiologic ligand, hepatocyte growth factor/scatter factor (HGF/SF) activates a series of downstream processes that are critical for oncogenesis including cell proliferation, survival, invasion/migration and metastasis.[31] Upon binding of HGF to the Sema domain of MET, dimerization and subsequent autophosphorylation occurs leading the activation of MET receptor and downstream signaling through the RAS-ERK, PI3K-AKT-mTOR and STAT pathways .[31] In addition, activated MET has been demonstrated to have significant crosstalk with the EGFR pathway.[31] Aberrant signaling through the MET pathway has been observed in a number of tumor types and can occur through mutation, amplification or overexpression of the *MET* or overexpression of *HGF*.[32] Although mutations in the *MET* gene are rare in NSCLC,[33] the *MET* gene is amplified in adenocarcinoma of the lung in 1% to 20% of cases examined.[34-36] Recently, a large study by the LCMC suggested the *MET* gene is only amplified in about 1% of adenocarcinomas of the lung.[37] Interestingly, *MET* amplification is a common mechanism of acquired resistance to EGFR TKIs and is found in up to 20% of patients who have acquired resistance to EGFR TKIs.[38,39] In addition to mutations or amplification of *MET*, the MET protein is overexpressed in a significant number of cases of advanced NSCLC.

Given the critical role of the MET pathway in tumorigenesis, metastasis and acquired resistance to targeted therapy, there are more than a dozen MET targeted therapies in clinic trials which target its ligand HGF (rilotumumab, ficlatuzumab), the extracellular portion of the MET receptor (onartuzumab – MetMAb) or the intracellular kinase activity of the MET receptor (tivantinib, crizotinib, cabozantinib).[32] Although anti-MET therapy as monotherapy or in combination in unselected patient populations has been disappointing to date, a recent phase II trial comparing onartuzumab (MetMAb) and erlotinib versus erlotinib alone in the 2nd and 3rd line setting for metastatic NSCLC found a significant advantage in PFS and OS for the combination in the "MET high" population.[40] Furthermore, 54% of patient samples were defined as "MET high" (50% or greater cells on the diagnostic slide with a staining intensity of 2 or 3) which suggests that a significant fraction of patients with metastatic lung cancer may be at least partially MET dependent. This concept is now being tested in global Phase III randomized, multicenter, double-blind, placebo-controlled study testing this combination vs. erlotinib only in the "MET high" population (NCT01456325). In addition to monoclonal antibodies targeting MET, there are several MET tyrosine kinase inhibitors in development and/or FDA approved agents (crizotinib), and these agents are being used to target the MET pathway in mutational defined subsets such as *KRAS* mutant NSCLC and in the acquired resistance to EGFR TKI therapy setting.[41] Of most significance to this protocol, several case reports have suggested that patient tumors with *MET* amplification may be MET "addicted" and dramatic responses have been seen with MET TKI monotherapy. [42, 43]

2.2 Drug Information: Cabozantinib (XL184)

Cabozantinib (XL184) is an inhibitor of multiple receptor tyrosine kinases and was approved by the U.S. Food and Drug Administration (FDA) on 29 November 2012 for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). It is commercially available as COMETRIQ® in the United States.

2.2.1 Pharmacology

Cabozantinib inhibits receptor tyrosine kinases MET (hepatocyte growth factor [HGF] receptor), vascular endothelial growth factor receptor 2 (VEGFR2), and RET. These targets are important mediators of tumor growth and/or angiogenesis, and MET is particularly associated with tumor invasiveness and metastasis. In vivo pharmacodynamic activity of cabozantinib against MET, VEGFR2 and RET has been demonstrated in preclinical studies and has been associated with tumor growth inhibition and tumor regression. In preclinical studies, cabozantinib treatment has also been shown to inhibit tumor angiogenesis, tumor invasiveness and metastasis, and the progression of tumors in bone.

2.2.2 Cabozantinib Nonclinical Toxicology

In nonclinical toxicology studies of cabozantinib in rodents and non-rodents, histopathological changes associated with cabozantinib administration were observed in gastrointestinal (GI) tract, bone marrow, lymphoid tissues, kidney, adrenal, and reproductive tract tissues, and secondary changes were observed in bone and pancreas. Cabozantinib tested negative in bacterial and mammalian cell genotoxicity assays in vitro. In reproductive toxicity studies, cabozantinib was embryotoxic in rats, produced fetal soft tissue changes in rabbits, and decreased fertility in male and female rats.

2.2.3 Clinical Experience and Summary

A range of cabozantinib dose levels have been explored. In Phase 1 Study XL184-001, subjects were treated with cabozantinib at doses ranging from 0.064 to 9.22 mg/kg (0.08 to 11.52 mg/kg malate salt weight) using a powder-in-bottle (PIB) aqueous suspension formulation on an intermittent dosing schedule; from 140 mg (175 mg malate salt weight) to 212 mg (265 mg malate salt weight) as a PIB formulation on a once-daily dosing (qd) schedule; and from 140 mg to 200 mg (250 mg malate salt weight) in capsule form on a qd schedule. Other studies have explored doses as low as 20 mg (25 mg malate salt weight). In more recently initiated clinical studies, cabozantinib is being administered in a tablet formulation. Results from a bioequivalence study in healthy adult subjects (Study XL184-010) indicate that the cabozantinib 140 mg tablet formulation is bioequivalent to the 140 mg capsule formulation based on AUC parameters (AUC from 0 hours to the last sampling time point [AUC0-t] and AUC from 0 hours to infinity [AUC0-∞] geometric mean ratios: 108%; 90% confidence interval (CI)%: 101, 117).

The single-agent maximum tolerated dose (MTD) of the capsule in a daily dosing schedule based on 28 days of dosing in Study XL184-001 was determined to be 140 mg (175 mg malate salt weight). The 140 mg capsule dose level was evaluated in placebo-controlled Phase 3 Study XL184-301 in subjects with MTC: dose modifications (reductions or interruptions) occurred frequently in the cabozantinib arm of this study.

Lower doses of cabozantinib have been explored in other indications, and two ongoing Phase 3 studies in prostate cancer are evaluating a tablet dose of 60 mg qd. Common to all approaches is the titration of the dose to individual patient tolerability. *Note: There is no allowance for dose escalations*

above 60 mg in the prostate cancer Phase 3 studies.

A pooled analysis of safety data in 1311 subjects treated with cabozantinib in company-sponsored single-agent studies (XL184-001, XL184-008, XL184-201, XL184-203, XL184-205, and XL184-301 [cabozantinib arm]) has been performed. The data cut-off for this analysis is 28 February 2013.

2.2.4 Clinical Safety Profile

2.2.4.1 Adverse Events

Across company-sponsored open-label studies with single-agent cabozantinib, the most frequently (≥ 20% of subjects) observed AEs, regardless of causality, are shown in Table 1-1.

Table 1-1: Summary of Adverse Events Experienced by ≥ 20% of Subjects Treated with Single-Agent Cabozantinib, N = 1311

	All AEs		Related AEs	
MedDRA Preferred Term	Subjects with AE n (%)	Subjects with ≥ Grade 3 AE n (%)	Subjects with AE n (%)	Subjects with ≥ Grade 3 AE n (%)
Number of subjects with at least one event	1305 (99.5)	1082 (82.5)	1271 (96.9)	822 (62.7)
Fatigue	875 (66.7)	208 (15.9)	786 (60.0)	177 (13.5)
Diarrhoea	827 (63.1)	146 (11.1)	736 (56.1)	127 (9.7)
Decreased appetite	680 (51.9)	70 (5.3)	578 (44.1)	49 (3.7)
Nausea	680 (51.9)	53 (4.0)	556 (42.4)	33 (2.5)
Weight decreased	472 (36.0)	60 (4.6)	382 (29.1)	46 (3.5)
Palmar-plantar erythrodysaesthesia syndrome	471 (35.9)	117 (8.9)	467 (35.6)	117 (8.9)
Vomiting	447 (34.1)	52 (4.0)	308 (23.5)	25 (1.9)
Constipation	435 (33.2)	22 (1.7)	221 (16.9)	6 (0.5)
Dysgeusia	367 (28.0)	1 (0.1)	355 (27.1)	1 (0.1)
Hypertension	364 (27.8)	127 (9.7)	315 (24.0)	116 (8.8)
Dysphonia	345 (26.3)	3 (0.2)	289 (22.0)	2 (0.2)
Abdominal pain	306 (23.3)	72 (5.5)	157 (12.0)	16 (1.2)
Aspartate aminotransferase increased	301 (23.0)	43 (3.3)	264 (20.1)	31 (2.4)
Dyspnoea	279 (21.3)	44 (3.4)	99 (7.6)	9 (0.7)
Headache	274 (20.9)	25 (1.9)	89 (6.8)	3 (0.2)
Rash	268 (20.4)	10 (0.8)	225 (17.2)	10 (0.8)
Alanine aminotransferase increased	265 (20.2)	48 (3.7)	237 (18.1)	43 (3.3)

AE, adverse event; MedDRA, Medical Dictionary of Regulatory Activities.

Note: This table summarizes pooled data in the clinical database for all single-agent cabozantinib studies (XL184-001, XL184-008, XL184-201, XL184-203, XL184-205, and XL184-301 cabozantinib arm).

2.2.4.2 Serious Adverse Events

Medically important adverse events (MIAEs) of Grade 3 and higher that may be related to cabozantinib, including gastrointestinal (GI) perforation (1.5%), GI fistula (0.5%) and non-GI fistula (0.6%) formation, intra-abdominal/pelvic abscess (0.9%), non-central nervous system (non-CNS) (3.1%) and CNS (0.8%) hemorrhage, venous (8.7%) and arterial (1.8%) thromboembolic events, wound complications (1.0%), hypertension (10.0%), osteonecrosis (0.2%), palmar-plantar erythrodysesthesia (PPE; 9.1%), proteinuria (1.4%), and hepatocellular toxicity (0.8%), have been observed in single-agent clinical studies with cabozantinib. A single event of reversible posterior leukoencephalopathy (RPLS) has occurred in one cabozantinib-treated subject in Study XL184-301.

The most commonly reported SAEs (experienced by ≥1% of subjects), regardless of causality, are shown in Table 1-2.

Table 1-2: Summary of Serious Adverse Events Experienced by ≥ 1% of Subjects Treated with Single-Agent Cabozantinib Excluding Events of Disease Progression[a], N = 1311

Preferred Term	Subjects with SAE n (%)	Subjects with Related SAE n (%)
Subjects reporting at least one SAE	**688 (52.5)**	**300 (22.4)**
Pulmonary embolism	67 (5.1)	52 (4.0)
Vomiting	45 (3.4)	18 (1.4)
Dehydration	42 (3.2)	24 (1.8)
Pneumonia	39 (3.0)	3 (0.2)
Nausea	39 (3.0)	22 (1.7)
Abdominal pain	31 (2.4)	6 (0.5)
Diarrhoea	31 (2.4)	24 (1.8)
Deep vein thrombosis	28 (2.1)	13 (1.0)
Convulsion	26 (2.0)	1 (0.1)
Dyspnoea	20 (1.5)	3 (0.2)
Hyponatraemia	18 (1.4)	8(0.6)
Back pain	18 (1.4)	1 (0.1)
Fatigue	17 (1.3)	11 (0.8)
Renal failure acute	17 (1.3)	2 (0.2)
Urinary tract infection	17 (1.3)	2 (0.2)
Mental status changes	16 (1.2)	1 (0.1)
Confusional state	16 (1.2)	4 (0.3)
Asthenia	15(1.1)	4 (0.3)
Anaemia	15 (1.1)	3 (0.2)
Pyrexia	15 (1.1)	1 (0.1)
Small intestine obstruction	14 (1.1)	0

MedDRA, Medical Dictionary or Regulatory Activities; SAE, serious adverse event.

Note: Reported SAEs were coded using MedDRA version 15.1.

Note: This table summarizes pooled data from the safety database for single-agent cabozantinib studies (XL184-001, XL184-008, XL184-201, XL184-203, XL184-205, and XL184-301 cabozantinib arm).

[a] Disease progression is expected for subjects with advanced cancer on cabozantinib clinical trials, and as such, events of progression of underlying cancer are not included

No cases meeting the Hy's law criteria have been identified as of 28 Feb 2013.
At the 140 mg dose, a mean increase from baseline in Fridericia's correction of QT (QTcF) of 10-15 ms was observed at 4 weeks (Day 29) after initiating cabozantinib treatment in Study XL184-301. No changes in cardiac wave form morphology or new rhythms were observed. No cabozantinib-treated subjects had a QTcF > 500 ms.

2.2.4.3 Deaths

There have been 24 deaths assessed as related to study treatment in the pooled analysis of single-agent studies: GI hemorrhage (two subjects), pulmonary embolism (PE) (two subjects), respiratory failure (two subjects), hemorrhage (two subjects), death due to unknown cause (three subjects); reasons for death in a single subject were intestinal perforation, diverticular perforation/peritonitis, hemoptysis/tracheal fistula, acquired tracheo-esophageal fistula, esophageal fistula, enterocutaneous fistula, esophageal hemorrhage, respiratory disorder, cardiac arrest, hepatic failure, sudden death, bronchopneumonia and sepsis.

In the Phase 1b/2 XL184-202 study evaluating combined dosing of cabozantinib/erlotinib, the MTDs were determined to be 40 mg (50 mg malate salt weight) of cabozantinib plus 150 mg of erlotinib (maximizing the erlotinib dose) and 100 mg (125 mg malate salt weight) of cabozantinib plus 50 mg of erlotinib (maximizing the cabozantinib dose). There was a higher incidence of diarrhea with combination treatment compared with single-agent cabozantinib.

In the Phase 1 XL184-002 dose-finding study evaluating 40 or 60 mg doses (50 or 75 mg malate salt weight, respectively) of cabozantinib in combination with standard dose TMZ ± radiation therapy there was a higher incidence of thrombocytopenia and neutropenia with combination treatment compared with single-agent cabozantinib. The MTD for cabozantinib in combination with TMZ was determined to be 40 mg qd.

2.2.5 Clinical Pharmacokinetics

From a population PK (PopPK) analysis of cabozantinib, the predicted effective half-life is approximately 55 hours, the oral volume of distribution (V/F) is approximately 349 L, and the clearance (CL/F) at steady-state is estimated to be 4.4 L/h. The terminal half-life (for predicting drug washout) is approximately 120 hours. Following oral administration of cabozantinib, median time to peak cabozantinib plasma concentrations (Tmax) ranged from 2 to 5 hours post-dose. Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in 4- to 5-fold mean cabozantinib accumulation (based on area under the plasma concentration-vs-time curve [AUC]) compared with a single dose administration; steady state was achieved by Day 15. Cabozantinib is highly protein bound in human plasma (≥ 99.7%).The PK evaluation of cabozantinib in the pediatric population is ongoing. A PopPK analysis did not identify clinically relevant differences in clearance of cabozantinib between females and males or between Whites (89%) and non-Whites (11% [<4% were Asian]). Cabozantinib PK was not affected by age (20-86 years).

Within a 48-day collection period after a single dose of 14C-cabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27%

in urine. A PK study of cabozantinib in patients with renal impairment is ongoing. The results of a population PK analysis suggested that mild to moderate renal impairment (creatinine clearance value ≥30 mL/min) does not have a clinically relevant effect on the clearance of cabozantinib.

A high-fat meal increased maximum plasma concentration (Cmax) and AUC values by 41% and 57%, respectively relative to fasted conditions in healthy subjects administered a single 140 mg oral cabozantinib dose.

Cabozantinib is a substrate of cytochrome P450 (CYP) 3A4 (CYP3A4) in vitro. Inhibition of CYP3A4 reduced the formation of the cabozantinib N-oxide metabolite by >80%. Inhibition of CYP2C9 had a minimal effect on cabozantinib metabolite formation (i.e., a <20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. Cabozantinib AUC was increased 38% with coadministration of the strong CYP3A4 inhibitor ketoconazole and decreased 77% with coadministration of the strong CYP3A4 inducer rifampin.

Cabozantinib is a noncompetitive inhibitor of CYP2C8 (Kiapp = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (Kiapp = 10.4 μM) and CYP2C19 (Kiapp = 28.8 μM), and a weak competitive inhibitor of CYP3A4 (estimated Kiapp = 282 μM) in human liver microsomal (HLM) preparations. Concentration associated with 50% inhibition (IC50) values >20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes in both recombinant and HLM assay systems. Cabozantinib at steady-state plasma concentrations (≥100 mg/day daily for a minimum of 21 days) showed no effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (Cmax and AUC) in patients with solid tumors.

Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations (i.e., 75-100% of CYP1A1 positive control β-naphthoflavone induction), but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities.

Cabozantinib is an inhibitor (IC50 = 7.0 μM), but not a substrate, of P-glycoprotein (P-gp) transport activities in a bi-directional assay system using MDCK-MDR1 cells.

Comparative Bioavailability Study of Cabozantinib Tablet and Capsule Formulations in Healthy Adult Subjects (Study XL184-005)
Study XL184-005 is a Phase 1, open-label, randomized, single-dose, two-treatment, two way crossover comparative bioavailability study of cabozantinib tablet and capsule formulations in healthy volunteers. Subjects received single oral doses of the assigned treatment of Test (100 mg cabozantinib, dosed as one 100 mg tablet) or Reference (100 mg cabozantinib, dosed as two 50 mg capsules), according to a randomization scheme. Each dosing was administered under fasting conditions, and blood samples were collected up to 504 hours post dose for each subject after each treatment to assess plasma cabozantinib PK.

Based on the preliminary PK data from 23 subjects who completed both treatments, after a single oral dose of cabozantinib at 100 mg, the terminal-phase half-life (t1/2, z) of cabozantinib appeared to be similar for both tablet and capsule formulations, with approximately mean values of 110 hours. The median time to the maximum plasma concentration (tmax) was 4 hours for the tablet formulation and

5 hours for the capsule formulation. High inter-subject variability for the maximum plasma concentration (Cmax) and the area under the plasma drug concentration time curve (AUC) values were observed for both formulations (coefficient of variation [CV]% Cmax: 51% for the tablet formulation, 61% for the capsule formulation; CV% for the AUC from time zero to the last quantifiable timepoint or to infinity [AUC0-last or AUC0-inf]: 40-43% for the tablet formulation, 43% for the capsule formulation.) The geometric mean Cmax of the tablet formulation was approximately 39% higher than the value observed for the capsule formulation. The geometric mean AUC0-last and AUC0-inf values for the tablet formulation were also higher (15% and 19%, respectively) than those observed for the capsule formulation. However, due to the high within-formulation variability observed, no statistical difference in exposure between the two formulations was apparent.

Effect of Food on the Bioavailability of Cabozantinib in Healthy Adult Subjects (Study XL184-004)
Study XL184-004 is a Phase 1, open-label, randomized, single-dose, two-treatment, two-way crossover study to assess the effect of food on the bioavailability of cabozantinib in healthy adult subjects. According to a randomization scheme, 56 subjects received single oral doses of the assigned treatment of Test (175 mg cabozantinib, dosed as one 100 mg capsule and three 25 mg capsules 30 minutes after administration of a high fat breakfast) or Reference (175 mg cabozantinib, dosed as one 100 mg capsule and three 25 mg capsules under fasting conditions). Blood samples were collected up to 504 hours post dose for each subject after each treatment to assess plasma cabozantinib pharmacokinetics.

Based on the preliminary PK data from 46 subjects who completed both treatments, a high fat meal did not appear to alter the terminal t1/2, z of cabozantinib [mean t1/2, z : 131 hours (fed) vs 128 hours (fasted)]. The high fat meal significantly increased the median tmax to 6 hours from 4 hours (fasted). The high fat meal also significantly increased both the cabozantinib Cmax and AUC values by 39% and 56%, respectively. The geometric mean ratio of Cmax fed/fasted was 1.39 (90% CI: 1.16-1.67), and the geometric mean ratio of AUC0-last fed/fasted was 1.56 (90% CI: 1.34-1.80). Based on this result, cabozantinib must be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each cabozantinib dose).

2.2.6 Clinical Activity

In addition to MTC, cabozantinib has demonstrated findings consistent with broad clinical anti-tumor activity in early Phase 1 and Phase 2 studies in several other tumor types. In a randomized discontinuation trial (RDT) XL184-203, the following disease control rates (DCR = complete response [CR] + partial response [PR] + stable disease [SD]) at Week 12 were observed in tumor types including non-small cell lung cancer (NSCLC), 38%; breast cancer, 48%; melanoma, 46%; ovarian cancer, 53%; hepatocellular carcinoma (HCC), 66%; and CRPC, 66%. In Study XL184-008, clinical activity was also observed in differentiated thyroid cancer (DTC; DCR = 73% at 24 weeks) and renal cell carcinoma (RCC; median progression-free survival [PFS] = 12.9 months). Observations of clinical activity have included decrease of soft tissue tumor lesions including visceral metastases, effects on metastatic lesions on bone scan (partial or complete bone scan resolution), reduction in serum markers of bone resorption and formation, reduction in circulating tumor cells (CTCs; subjects with prostate cancer), increases in hemoglobin, and improvements in bone pain and reductions in

narcotic use in subjects with bone metastases. Activity in MTC and CRPC subjects is described in more detail below.

In the placebo-controlled Phase 3 study XL184-301 in 330 MTC subjects, a significant increase in median PFS was seen in the cabozantinib arm compared with placebo (11.2 vs 4.0 months; hazard ratio [HR] =0.28; 95 CIs: 0.19, 0.40). Confirmed PRs occurred in 28% of cabozantinib-treated subjects and none in the placebo arm; responses were durable (median duration 14.6 months). An unplanned administrative analysis of overall survival (OS) performed at the request of the FDA with a data cut-off of 15 June 2012 (75% of required deaths) showed a trend for improved duration of OS in the cabozantinib arm compared with placebo (26.0 months vs 20.3 months; HR = 0.83; 95% CI: 0.60, 1.14).

2.2.6.1 XL184-001

In a Phase 1 study (XL184-001), subjects with advanced tumors were enrolled in successive cohorts to receive cabozantinib administered orally (PO) as capsules or as a PIB aqueous suspension formulation. A total of 85 subjects, including 37 subjects with MTC, were enrolled in the XL184-001 study. Among the 35 subjects with MTC and measurable disease, PR was achieved in 10 subjects (29%): three subjects were treated at starting dose levels other than the MTD of 140 mg (175 mg malate salt weight) capsule formulation and seven subjects were treated at the MTD. Five of the 10 responders had a PR at the first radiologic assessment. The median duration of treatment for these 10 subjects was 538.5 days (17.7 months) with a range of 145 to 2082+ days (4.8 to 68.4+ months). Activity was independent of both RET mutation status and prior treatment with tyrosine kinase inhibitors, including those known to inhibit RET (e.g., vandetanib) (Kurzrock et al. 2011).

2.2.6.2 XL184-201

In a Phase 2 study (XL184-201), subjects with relapsed or recurrent GB in first or second relapse were enrolled to receive cabozantinib qd as a single agent. Subjects were enrolled in three successive cohorts, the first receiving an initial dose of 140 mg FBE weight (175 mg malate salt weight; Group A). To explore the tolerability and antitumor activity at a lower dose, subsequent cohorts (Groups B and C) received an initial dose of 100 mg (125 mg malate salt weight). Study objectives included assessments of safety, tolerability, and clinical activity (consisting of independent radiology facility [IRF]-determined response assessment and PFS), at the two dose levels.

Clinical activity data are summarized in Table 1-3 for 46 subjects who received cabozantinib at a starting dose of 140 mg (175 mg malate salt weight) qd (Group A) and 59 subjects who received cabozantinib at a starting dose of 100 mg (125 mg malate salt weight) qd (Group B). In both of these cohorts, radiographic response was evaluated by an IRF review of MRI scans per modified Macdonald criteria (Macdonald et al. 1990). An additional cohort with a starting dose of 100 mg qd (Group C) was also enrolled, but clinical activity data have not yet been analyzed.

Table 1-3: Response Rate and Progression-Free Survival in XL-184-201 (N=105)

	Prior Anti-Angiogenic Treatment			
	Naïve		Pretreated	
Group	A (n = 34)	B (n = 37)	A (n = 12)	B (n = 22)
Dose	140 mg	100 mg	140 mg	100 mg
ORR, n (%)[a]	7 (21)	11 (30)	1 (8)[b]	0
Median duration of response, months (range)[a]	2.9 (1.9-12.8)	5.1 (0.9+ - 6.7+)	NE	NE
Median progression-free survival, weeks[c]	15.9	16.0	14.3	7.9
Progression-free survival at 6 months, %[c]	10	25	38	0

IRF, independent radiology facility; NE, not estimable; ORR, objective response rate.
[a] Per IRF
[b] Duration of response = 12.3 months (subject previously treated with vandetanib)
[c] Per investigator

2.2.6.3 XL184-202

In a Phase 1b/2 study (XL184-202), subjects with NSCLC received treatment with cabozantinib with or without erlotinib. The Phase 1 portion of the study followed a dose-escalation design in which subjects with NSCLC in whom erlotinib therapy had failed were enrolled in successive cohorts to receive once-daily doses of cabozantinib in combination with erlotinib. During the Phase 1 portion of the study, erlotinib was administered as a single agent for a 14-day run-in phase, and then cabozantinib and erlotinib were administered in combination for 28-day cycles. Dosing cohorts were assessed in two parallel arms maximizing doses of cabozantinib and erlotinib. The MTD of Arm A (maximizing the erlotinib dose) was determined to be 100 mg FBE weight (125 mg malate salt weight) of cabozantinib plus 50 mg of erlotinib. The MTD of Arm B (maximizing the cabozantinib dose) was determined to be 40 mg (50 mg malate salt weight) of cabozantinib plus 150 mg of erlotinib.

In the Phase 2 portion of the study, subjects with NSCLC who had progressed after receiving clinical benefit from erlotinib were enrolled in two parallel arms: Arm 1 in which treatment was single-agent cabozantinib at a dose of 100 mg qd and Arm 2 in which treatment comprised cabozantinib in combination with erlotinib at a dose of cabozantinib 100 mg and erlotinib 50 mg (the MTD of Arm A from the Phase 1 portion). Twenty-eight subjects (15 in Arm 1 and 13 in Arm 2) received study drug in Phase 2. Enrollment of this study has been terminated. Clinical and safety data for this study is available through the database cut-off date of 02 August 2012.

Sixty-four subjects were enrolled in the Phase 1 dose-escalation portion of the study examining the combination of cabozantinib and erlotinib in NSCLC subjects. All but two subjects had been previously treated with and progressed on erlotinib therapy. A PR was observed in 5 subjects (8%). The ORR for the Phase 1 population was 8.2% (90% CI: 3.3, 16.5). The median PFS for subjects (mITT Population) was 3.68 months (95% CI: 3.15, 5.49). The Kaplan-Meier estimate of the probability of a subject to be progression-free at 6 months was 29.4%.

Twenty-eight subjects were enrolled in the Phase 2 portion of the study, in which subjects who had received clinical benefit from erlotinib and subsequently experienced PD receive single-agent cabozantinib or cabozantinib in combination with erlotinib. A PR was observed in one subject who was treated with single-agent cabozantinib. The ORR for subjects who received cabozantinib was 6.7% (90% CI: 0.3, 27.9). No objective responses were seen in subjects who received cabozantinib + erlotinib (0/13 subjects).

The median PFS for subjects (mITT Population) was 1.91 months (95% CI: 1.64, 7.06) for the cabozantinib arm and 3.94 months (95% CI: 1.54, 7.26) for the cabozantinib + erlotinib arm. The Kaplan-Meier estimate of the probability of a subject to be progression-free at 6 months was 30.8% for the cabozantinib arm and 22.0% for the cabozantinib + erlotinib arm.

2.2.6.4 XL184-203

In a Phase 2 RDT (XL184-203), subjects were enrolled into one of the nine tumor-specific cohorts: breast cancer, gastric/gastroesophageal junction (GEJ) cancer, HCC, melanoma, NSCLC, ovarian cancer, pancreatic cancer, prostate cancer, and small-cell lung cancer (SCLC). Eligible subjects with advanced solid tumors received open-label cabozantinib at a starting dose of 100 mg qd for 12 weeks (Lead-In Stage). Tumor response per mRECIST v1.0 was assessed every 6 weeks. Subjects with PR or CR at Week 12 continued to receive open-label cabozantinib; subjects with progressive disease (PD) discontinued cabozantinib. Subjects with SD at Week 12 were randomized 1:1 in a double-blinded fashion to receive cabozantinib or placebo (Randomized Stage). Cross-over from placebo to cabozantinib was allowed upon PD. Primary endpoints were objective response rate (ORR) at Week 12 and PFS in the Randomized Stage. An Independent Data Monitoring Committee (IDMC) monitored safety in the blinded Randomized Stage. As of October 2011, all subjects have been unblinded.

A Study Oversight Committee (SOC) monitored efficacy during the Lead-In Stage and, based on periodic review of all available data, could recommend that enrollment into specific cohorts be halted, continued within the RDT design, or closed in favor of opening an open-label NRE cohort. Non-randomized expansion cohorts were opened for CRPC (N=144) and ovarian cancer (N=61). Subjects enrolled into NRE cohorts received open-label cabozantinib qd until PD or unacceptable toxicity developed.

A total of 205 subjects received study drug in the NRE cohorts. In the CRPC cohort subjects were dosed at starting levels of either 100 mg (N=93) or 40 mg (N=51). All subjects (N=61) in the ovarian cancer cohort were dosed at the starting level of 100 mg.

In the Phase 2 study XL184-203, cabozantinib demonstrated broad clinical activity in men with CRPC (Smith et al. 2013). During the RDT phase, the majority of CRPC subjects with bone metastases and elevated total alkaline phosphatase (t-ALP) levels at baseline showed reductions in t-ALP (Smith et al. 2013). Similarly, during the non-randomized expansion (NRE) phase, the majority of CRPC subjects at the 100 mg assigned dose showed reductions in circulating bone specific alkaline phosphatase (BSAP) (Smith et al. 2012). These effects were independent of prior or concomitant bisphosphonate treatment. Reductions in bone biomarkers were also evident in the 40 mg CRPC NRE

cohort (de Bono et al, 2012). Effects on bone scan were assessed by an independent reader, and pain and narcotic use were prospectively assessed using an interactive voice recording system (IVRS) and a diary. Subjects achieved a bone scan response (BSR) in both the 100 mg and 40 mg assigned NRE dose cohorts (67% and 49%, respectively). Among subjects with baseline pain of at least 4 (0-10 scale by Brief Pain Inventory [BPI]), a majority had at least a decrease of 30% in the average daily worst pain compared with baseline in both cohorts (100 mg: 64% of subjects; 40 mg: 69% of subjects). In addition, more than half of subjects decreased narcotic use.

All enrolled subjects with hepatocellular carcinoma were Child-Pugh Class A, and 30 (73%) had evidence of extrahepatic spread. The majority of subjects (80%) had one to two lines of prior therapy. More than half of the subjects (51%) had been treated previously with sorafenib. The overall DCR at Week 12 was 66%. Regression of measurable soft-tissue disease per mRECIST was observed in 28 of 36 (78%) subjects with at least one post-baseline tumor assessment. Two subjects (5%) achieved PRs. Nine of 26 (35%) subjects who had alpha-fetoprotein (AFP) levels ≥ 20 ng/mL at baseline experienced ≥ 50% reduction in AFP. The overall median PFS was 4.4 months, while the sorafenib pre-treated group had a median PFS of 5.2 months. In an updated analysis, the median OS was 11.5 months (95% CI: 7.3, 15.6) (data on file). Among sorafenib-pretreated subjects, the median OS was 12.9 months (95% CI: 10.8, 16.8). Based on preliminary analysis, no apparent difference in cabozantinib exposure between subjects with HCC and subjects with other tumors was observed.

In unselected NSCLC patients, cabozantinib given at 100 mg orally daily was associated with a 10% ORR, a median PFS of 4.2 months and a 38% DCR at 12 weeks.

2.2.6.5 Translational Medicine

Phase 1: Study XL184-001: Exposure to cabozantinib resulted in significant changes in levels of the circulating biomarkers placental growth factor (PlGF), VEGF, soluble VEGFR2 (sVEGFR2), and erythropoietin (EPO), consistent with results observed with other anti-VEGFR2 pathway agents (Murukesh et al. 2010; Deprimo et al. 2007). Calcitonin (CTN) and carcinoembryonic antigen (CEA) levels in subjects with MTC have been found to correlate with tumor burden, and doubling times with risk of PD (Giraudet et al. 2007). There were clear treatment-related reductions in both markers in the majority of subjects with MTC treated with cabozantinib. While there was no obvious relationship between down-regulation of these markers and attaining a PR by investigator assessment, there was a weak but statistically significant correlation between best tumor response (% decrease in sum of longest diameter) and best calcitonin or best CEA response. It is unclear at this time whether these markers will have utility in monitoring response to cabozantinib in this disease setting.

Phase 2: Study XL184-201 (Glioblastoma): Plasma samples were analyzed for several biomarkers of response to anti-angiogenic agents, including levels of VEGF-A, sVEGFR2, and PlGF. Changes in pharmacodynamic markers consistent with cabozantinib on-target effects were observed after cabozantinib administration in 40 subjects treated with a starting dose of 140 mg FBE weight (175 mg malate salt weight). Changes in PlGF (↑), VEGF-A (↑), sVEGFR2 (↓), and soluble KIT (sKIT)(↓) reached statistical significance at multiple time points, particularly Days 15 and 29. Soluble MET as a potential biomarker of MET inhibition was modulated (↑) upon cabozantinib treatment and changes reached statistical significance as well, on Day 15 and Day 57 (Cycle 3 Day 1). Preliminary analysis of potential correlations between clinical outcome and baseline levels or changes during treatment of

the plasma proteins did not reveal significant correlations.

Results from a similar analysis of plasma samples obtained from subjects treated with a starting dose of 125 mg showed statistically significant modulation of plasma biomarkers VEGF-A, PlGF, and sVEGFR2, as well as modulation of sKIT and sMET.

Genotyping of Archival Tumor Tissue: Select genotyping analyses have been conducted on archival tumor tissue and clinical sites have shared their own results when available. Based on the preliminary analysis of 48 melanoma subjects with both tumor response and BRAF mutation data, clinical activity of cabozantinib appears to be independent of BRAF mutation status (Gordon et al. 2012). Clinical activity of cabozantinib also appears to be independent of epidermal growth factor receptor (EGFR) and KRAS mutation status in NSCLC subjects based on the preliminary data (Hellerstedt et al. 2012).

2.3 Rationale for the Study, Dose and Schedule

Seventeen to thirty percent of patients with newly diagnosed NSCLC will present with metastatic disease to the brain.[1-3] Treatment options for brain metastases from NSCLC include whole–brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), surgical resection or some combination of these options. The median survival time after whole-brain radiation therapy usually ranges from 3-6 months and strongly correlates with the patient's age, performance status, number and location of metastatic lesions. [4-6] In addition, whole brain radiotherapy may cause devastating CNS damage. The majority of patients with brain metastases also suffer from active extracranial disease, and systemic disease progression is a common cause of death. Therefore, development of effective systemic treatment for control of both extracranial and brain metastases is desirable.

There are an increasing number of drug trials that are specifically focusing on patients with brain metastases. One of possibly targetable pathways is *HGF/MET* pathway. The c-MET receptor tyrosine kinase has been implicated in tumor cell migration, invasion, proliferation and angiogenesis and is the only known high affinity receptor for hepatocyte growth factor (HGF).[7] Amplification of *c-MET* has been associated with poor prognosis in NSCLC, mediastinal lymph node metastases, and resistance, both acquired and intrinsic, to *EGFR* tyrosine kinase inhibitors in *EGFR*-mutant lung adenocarcinoma.[8-10] c-MET expression and phosphorylation has been shown to be associated with the development of NSCLC brain metastases and are selectively enriched in brain metastases relative to paired primary lung tumors.[11] Of most importance, the presence of *de novo c-MET* amplification in NSCLC has been linked to rapid and durable clinical response to single agent crizotinib, a c-MET receptor tyrosine kinase inhibitor.[12]

In a series of 200 NSCLC brain metastases collected at the University of Pittsburgh Medical Center (UPMC) between 2005 and 2012, 50% were of adenocarcinoma histology. To date we have completed FISH studies on 77 of these brain metastases. Twenty-one percent (16 of 77) of these brain metastases were *c-MET* amplified as defined by a FISH ratio > 2.0; 38% (6 of 16) of these *c-MET* amplified brain tumors also harbored a *KRAS* mutation (confidential unpublished data). These data are intriguing in its marked inconsistency with the ongoing genotyping efforts of the Lung Cancer Mutation Consortium (LCMC), in which *c-MET* amplification was present in only 5 (1%) of 733 metastatic lung adenocarcinomas that underwent profiling for 10 oncogenic drivers. Furthermore,

96% of the oncogenic drivers identified through the LCMC were mutually exclusive. These data suggest that *c-MET* amplification plays a critical role in the metastatic potential of NSCLC to the brain and implicates *c-MET* as a therapeutic target in NSCLC with brain metastases, in particular, the subset with *c-MET* amplification.

Cabozantinib (XL184) is a potent oral inhibitor of MET, VEGFR2, and RET that produces robust antiangiogenic and antitumor effects in preclinical models. The efficacy of single agent cabozantinib was evaluated in patients with progressive glioblastoma multiforme (GBM) in a phase II open-label clinical trial at 140 mg daily and 100 mg daily dose levels. Cabozantinib at both dose levels was associated with objective responses in central nervous system disease. The objective response rates (ORR) in patients who were naïve to prior treatment with anti-angiogenic therapy were 21% and 30%, at the 140 mg and 100 mg dose levels, respectively, suggesting blood-brain barrier penetration. In a randomized discontinuation study in unselected NSCLC patients, cabozantinib given at 100 mg orally daily was associated with a 10% overall response rate (ORR) and an overall disease control rate (partial response plus stable disease) of 40%. This current trial is a single-arm phase II clinical trial evaluating the efficacy and safety of cabozantinib in NSCLC patients with brain metastases both in an unselected population and in a subset with *c-MET* amplification.

A starting dose of cabozantinib 60 mg daily was selected based on an expected better toxicity and tolerability profile. Cabozantinib 140 mg daily in GBM is most commonly associated with fatigue (any grade) in 74% patients (grade 3/4 fatigue in 30% patients). Adverse side effects (all grades) associated with dose reduction/interruptions were asthenia in 24% patients, palmar-plantar erythrodysesthesia in 17% patients, anorexia in 13% patients, diarrhea in 13% patients, transaminase elevations in 11% patients, nausea in 9% patients, and pancreatitis/pancrease enzyme increase in 9% patients. In total, cabozantinib 140 mg daily was associated with dose interruptions in 87% patients and dose reductions in 52% patients. Cabozantinib 100 mg daily is better tolerated with grade 3/4 fatigue occurring in 16% patients (any grade, 63% patients). The most common all-grade adverse events were a variable cluster of symptoms consisting of fatigue, decreased appetite, taste alterations, nausea, diarrhea, weight loss, and palmar-plantar erythrodysesthesia, which resulted in dose reductions in 62% of patients. [44] However, 60 mg is the recommended phase II dose in a clinical trial enrolling NSCLC patients in Japan, and 60 mg is the starting dose of cabozantinib in a number of ongoing clinical trials for other tumor indications as well.

2.4 Study Design

2.4.1 Overview of Study Design

This is a Phase 2, single-arm, open-label study of cabozantinib in subjects with molecularly unselected NSCLC with metastases to the brain and in patients with *c-MET* amplified NSCLC with metastases to the brain.

Patients will receive cabozantinib at 60 mg once daily and continue on treatment until disease progression, death or unacceptable adverse events. Treatment cycles are 4 weeks in duration.

The primary endpoint is ORR in both the unselected NSCLC population and the molecularly selected patients on the basis of *c-MET* amplification.

Simon's optimal two-stage design is used to minimize the expected sample size if the treatment is not effective. A stopping rule for futility is implemented if 1 or fewer of the first 29 patients have an objective response. (Accrual may continue during follow-up for these patients.) If ≥2 responses are observed in the first 29 patients, an additional 25 patients will be enrolled. A promising study result would be a response rate of 6/54 (11%) or greater. This design has 82% power to detect a true response rate of 15% (compared with a null rate of 5%). A minimum of 15 evaluable patients with *c-MET* amplified tumors will be enrolled. If 1 or fewer than 29 patients in the first stage of the Simon design have an objective response and the minimum number of c-MET amplified tumors has not been met, accrual will continue for the *c-MET* amplified subset only, until the minimum number of patients with *c-MET* amplified tumors is met.

3. PATIENT SELECTION

3.1 Eligibility Criteria

A subject must fully meet all of the following criteria to be eligible for enrollment as defined by the inclusion and exclusion criteria as follows:

1. Previously treated patients with non-squamous NSCLC who have had brain metastases at any point in their treatment history are eligible for enrollment on this clinical trial. (Patients must have received at least one regimen for systemic disease which may be cytotoxic or oral tyrosine kinase inhibitor therapy.)
    a. Patients with clinically asymptomatic (no requirement for systemic corticosteroids) untreated brain metastases will be allowed on trial at the discretion of the treating physician
    b. Patients who have undergone treatment for their brain metastases with whole brain radiotherapy, stereotactic radiosurgery, or surgical resection must be clinically stable and recovered from all procedures at the time of study enrollment.
2. Patients must have tumor tissue available for submission that is sufficient to complete c-MET FISH studies as well as routine molecular profiling at the UPMC. Patients must agree to submission of these specimens as defined in Section 9.
    a. c-MET amplification will be determined by FISH ratio (c-MET/CEP7) > 2.0, based on testing of the primary tumor and/or site of metastatic disease
    b. Patients' tumors must undergo testing for EGFR exon 19 deletion, EGFR exon 21 L858R substitution, and ALK rearrangements. If positive, patients must have been treated with an appropriate TKI prior to enrolling to the study.
3. The subject has had an assessment of all extracranial disease sites (e.g., by computerized tomography (CT) scan, positron emission tomography-CT, and bone scan as appropriate) within 28 days before the first dose of cabozantinib.
4. The subject must have a baseline brain MRI scan or CT scan of the head (in patients unable to obtain an MRI) within 14 days prior to first dose of cabozantinib.

a. Patients receiving glucocorticoids must be on a stable dose of glucocorticoids during the 5 days prior to the baseline brain imaging.

5. Patients must have measurable disease as defined by RECIST v1.1
    a. Lesions that have previously been treated with SRS are excluded as measurable disease because distinction of radiation necrosis and tumor progression can be difficult in this setting and enlargement of the lesion may not necessarily mean progression.
6. Subjects having undergone recent resection or biopsy of an intracranial tumor will be eligible as long as all of the following conditions apply:
    a. First dose of cabozantinib occurs at least 28 days after surgery, and the subject has recovered from the effects of surgery
7. Age ≥18 years. Because no dosing or adverse event data are currently available on the use of cabozantinib in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.
8. ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).
9. Patients must have normal organ and marrow function as defined below: (within 4 days of beginning treatment unless noted otherwise)

Hemoglobin	≥9 g/dL
Absolute Neutrophil Count(ANC)	≥1,500/mm^3 (no CSF support)
Platelets	≥100,000/mm^3
Bilirubin	≤ 1.5 x upper limit of normal (ULN)
Bilirubin (Gilbert's Disease)	≤ 3.0 mg/dL
AST(SGOT) and ALT(SGPT)	≤3.0 × ULN
Serum creatinine OR Creatinine clearance (CrCl) For creatinine clearance estimation, the Cockcroft and Gault equation should be used: Male: CrCl (mL/min) = (140 - age) × wt (kg) / (serum creatinine × 72) Female: Multiply above result by 0.85	≤ 1.5 x ULN ≥40 mL/min
Lipase no radiologic or clinical evidence of pancreatitis	< 2.0 x ULN
Urine protein/creatinine ratio (UPCR)	≤1
Serum phosphorus, calcium, magnesium and potassium	≥ Lower limit of normal (LLN)

10. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document.
11. Women of childbearing potential must have a negative serum pregnancy test at screening. Women of childbearing potential include women who have experienced menarche and who

have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are not postmenopausal. Post-menopause is defined as amenorrhea ≥ 12 consecutive months. Note: women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, ovarian suppression or any other reversible reason.

12. The effects of cabozantinib on the developing human fetus are unknown. For this reason women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for 4 months after the last dose of study drug, even if oral contraceptives are used. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of cabozantinib administration.

3.2 Exclusion Criteria

1. The subject has received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (e.g., cytokines or antibodies; including investigational biologic agents) within 3 weeks, or nitrosoureas/ mitomycin C within 6 weeks before the first dose of study treatment.
2. The subject has received prior treatment with a small molecule kinase inhibitor or a hormonal therapy (including investigational kinase inhibitors or hormones) within 7 days or five half-lives of the compound or active metabolites, whichever is longer, before the first dose of study treatment.
3. Prior treatment with cabozantinib.
4. The subject has received radiation therapy as follows:
    a. To the thoracic cavity, abdomen or pelvis within 3 months of the first dose of study treatment or has with ongoing complications or is without complete recovery and healing from prior radiation therapy
    b. To bone or brain metastasis within 14 days of the first dose of study treatment
    c. To any other site(s) within 28 days of the first dose of study treatment
5. The subject has received radionuclide treatment within 6 weeks of the first dose of study treatment.
6. The subject has evidence of acute intracranial or intratumoral hemorrhage either by MRI or computerized tomography (CT) scan. The subject has not recovered to baseline or CTCAE ≤ Grade 1 from toxicity due to all prior therapies except alopecia and other non-clinically significant AEs.

7. The subject has prothrombin time (PT)/ International Normalized Ratio (INR) or partial thromboplastin time (PTT) test ≥ 1.3 × the laboratory ULN within 7 days before the first dose of study treatment.
8. The subject is receiving concomitant anticoagulation treatment at therapeutic doses with oral anticoagulants (e.g., warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (e.g., clopidogrel) at the time of study entry.

   Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (< 1 mg/day), and low dose, low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects without radiographic evidence of brain metastasis, who are on a stable dose of LMWH for at least 12 weeks before randomization, and who have had no complications from a thromboembolic event or the anticoagulation regimen.
9. The subject has received enzyme-inducing anti-epileptic agents within 2 weeks before the first dose of cabozantinib (e.g., carbamazepine, phenytoin, phenobarbital, primidone). Other enzyme inducing agents prohibited within 2 weeks before the first dose of cabozantinib include rifampin, rifabutin, rifapentin, and St. John's Wort.
10. The subject has experienced any of the following:
    a. Clinically-significant gastrointestinal bleeding within 6 months before the first dose of study treatment
    b. Hemoptysis of ≥ 0.5 teaspoon (2.5ml) of red blood within 3 months before the first dose of study treatment
    c. Any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment
11. The subject has radiographic evidence of cavitating pulmonary lesion(s)
12. The subject has tumor abutting, invading or encasing any major blood vessels.
13. The subject has evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib.
14. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    a. Cardiovascular disorders including
        i. Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening
        ii. Concurrent uncontrolled hypertension defined as sustained BP > 140 mm Hg systolic, or > 90 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment
        iii. Any history of congenital long QT syndrome
        iv. Any of the following within 6 months before the first dose of study treatment:
            1. unstable angina pectoris

2. clinically-significant cardiac arrhythmias
3. stroke (including TIA, or other ischemic event)
4. myocardial infarction
5. thromboembolic event requiring therapeutic anticoagulation (Note: subjects with a venous filter (e.g. vena cava filter) are not eligible for this study)

b. Gastrointestinal disorders particularly those associated with a high risk of perforation or fistula formation including:
   i. Any of the following within 28 days before the first dose of study treatment
      1. Intra-abdominal tumor/metastases invading GI mucosa
      2. Active peptic ulcer disease,
      3. Inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis
      4. Malabsorption syndrome
   ii. Any of the following within 6 months before the first dose of study treatment:
      1. Abdominal fistula
      2. Gastrointestinal perforation
      3. Bowel obstruction or gastric outlet obstruction
      4. Intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib even if the abscess occurred more than 6 months before the first dose of study treatment.
c. Other disorders associated with a high risk of fistula formation including PEG tube placement within 3 months before the first dose of study therapy.
d. Other clinically significant disorders such as:
   i. Serious active infection requiring systemic treatment within 28 days before the first dose of study treatment.
   ii. Serious non-healing wound/ulcer/bone fracture within 28 days before the first dose of study treatment.
   iii. History of organ transplant
   iv. Concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of study treatment.
   v. History of surgery as follows:
      1. Subjects having undergone recent resection or biopsy of an intracranial tumor will be eligible as long as all of the following conditions apply: First dose of cabozantinib occurs at least 28 days after surgery, and the subject has recovered from the effects of surgery.
      2. Other minor surgery within 28 days of the first dose of cabozantinib if there were no wound healing complications. If there is evidence of

wound dehiscence, subjects will be eligible for trial after a minimum of 3 months after surgery to the first dose of cabozantinib, provided complete wound healing is confirmed at least 28 days before the first dose of cabozantinib.

3. Other major surgery within 2 months of the first dose of cabozantinib if there were no wound healing complications. If there is evidence of wound dehiscence, subjects will be eligible for trial after a minimum of 6 months after surgery to the first dose of cabozantinib, provided complete wound healing in confirmed at least 28 days before the first dose of cabozantinib.

15. The subject is unable to swallow tablets.
16. The subject has a corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms within 28 days before randomization. Note: if initial QTcF is found to be > 500 ms, two additional EKGs separated by at least 3 minutes should be performed. If the average of these three consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard.
17. The subject is pregnant or breastfeeding.
18. The subject has a previously identified allergy or hypersensitivity to components of the study treatment formulation.
19. The subject is unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.
20. The subject has had evidence within 2 years of the start of study treatment of another malignancy which required systemic treatment. Note: Subjects with a history of early stage or locally advanced non-metastatic prostate cancer within 2 years of the start of study treatment may be included in the study.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

3.4 Replacements

Subjects will not be replaced in this study

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally at the Hillman Cancer Center by the Study Coordinator 412-623-3082.

Following registration, patients should begin protocol treatment within 28 days. Additional testing

will take place 4 days prior to the first dose of study treatment. Issues that would cause treatment delays should be discussed with the Investigator. If a patient does not receive protocol therapy following registration within the designated time period, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

To register a patient, the following documents should be completed by the research nurse, the PI or a co-investigator and faxed to 412-623-7862 at the Hillman Cancer Center

- Copy of required pre-study tests
- Completed eligibility checklist
- Signed patient consent form

The research nurse or data manager at the participating site will then call or e-mail the Study Coordinator, 412-623-3082, to verify eligibility. To complete the registration process, the Coordinator will

- Assign a patient study number
- Register the patient on the study
- Fax or e-mail the patient study number to the participating site
- Call the research nurse or data manager at the participating site and verbally confirm registration.

5. TREATMENT PLAN

5.1 Agent Administration: Cabozantinib Tablets (XL-184)

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose reduction is described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description				
Agent	***Dose***	***Route***	***Schedule***	***Cycle Length***
Cabozantinib	60mg	orally	7 days per week	28 days (4 weeks)
The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each 28 day cycle.				

Subjects will receive cabozantinib at 60 mg (starting dose) once daily and continue treatment until disease progression or death, see section 5.4, or unacceptable adverse event as defined in section 7. Cabozantinib is to be taken without food (subjects should not eat for at least 2 hours before and at least 1 hour after taking cabozantinib) with a full glass (at least 8 ounces) of water.

5.2 General Concomitant Medication and Potential Drug Interactions

5.2.1 Anticancer Therapy

If a subject requires additional systemic anticancer treatment, including steroid treatment for prostate cancer subjects, study treatment must be discontinued. Local intervention is discouraged unless medically unavoidable. Subjects receiving local intervention (e.g., palliative radiation) are allowed to continue to receive study treatment at the investigator's discretion. Subjects with prostate cancer currently receiving luteinizing hormone-releasing hormone (LHRH) or gonadotropin releasing hormone (GnRH) agonists may be maintained on these agents.

5.2.2 Other Medications

Subjects must be instructed to inform the investigators of the current or planned use or all other medications during the study (including prescription medications, vitamins, herbal and nutritional supplements, and over-the-counter medications). It is the responsibility of the investigator to ensure that details regarding all medications are documented.

Bisphosphonates started prior to screening activities or initiated during the course of the study to control bone pain are allowed with caution.

Colony stimulating factors (e.g., erythropoietin and granulocyte colony stimulating factors) and pain medications administered as dictated by standard practice are acceptable while the subject is enrolled in the study. However, colony stimulating factors should not be administered prophylactically prior to the first dose of study treatment.

No concurrent investigational agents are permitted.

5.2.3 Potential Drug Interactions

Cytochrome P450: Preliminary data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the AUC of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared to CYP2C8 (i.e., CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate (but not a CYP2C9 or CYP2D6 substrate), based on data from

in vitro studies using CYP-isozyme specific neutralizing antibodies.

Preliminary results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 80% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib e.g., chronic use of modafinil should be avoided because of its potential to reduce cabozantinib exposure. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended. In addition, caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Preliminary results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 33-39% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations. Grapefruit / grapefruit juice and Seville oranges may also increase plasma concentrations of cabozantinib. Strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Because in vitro studies only assessed the metabolizing capacity of the CYP3A4, CYP2C9, and CYP2D6 pathways, the potential for drugs that inhibit/induce other CYP450 pathways (e.g., CYP2C8, CYP2C19, CYP2B6, CYP1A2) to alter cabozantinib exposure is not known. Therefore, these drugs should be used with caution when given with cabozantinib.
Please refer to the Flockhart drug interaction tables for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways (Flockhart 2007; http://medicine.iupui.edu/clinpharm/ddis/table.aspx).

Protein Binding:
Cabozantinib is highly protein bound (approximately 99.9%) to human plasma proteins. Therefore, highly protein bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib. Therefore, concomitant medications that are highly protein bound (e.g., diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution. Because warfarin is a highly protein bound drug with a low therapeutic index, administration of warfarin at therapeutic doses should be avoided in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.

Drugs Associated with QTc Prolongation:
Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Caution should be used when treating subjects on cabozantinib with other drugs associated with QTc prolongation (see http://www.qtdrugs.org). Additional QTc monitoring is suggested for subjects who are treated concomitantly with QTc prolonging drugs.

Other Interactions:
In a relative bioavailability study in dogs, cabozantinib exposure was not significantly affected by drugs that alter gastric pH. Nevertheless, drugs such as proton pump inhibitors (PPIs) and H2 antagonists produce profound suppression of gastric acid secretion and significant increases in gastric pH. By elevating gastric pH, PPIs and H2 antagonists may decrease cabozantinib plasma exposure levels and its effectiveness in vivo, resulting in clinically significant drug interactions. The use of PPIs (e.g., omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole) and/or H2 antagonists (e.g., ranitidine, famotidine, and nizatidine) is discouraged during this study. If antacids are not adequate, the use of H2 blockers is preferred over PPIs (Note: Cimetidine should be avoided because of its potential to interfere with CYP3A4 mediated metabolism of cabozantinib). Antacids, H2 blockers, or PPIs should be taken at least 2 hours (preferably 4 hours) after taking cabozantinib but at least 14 hours before the next dose of cabozantinib if possible.

In vitro data suggest that cabozantinib is unlikely to be a substrate for P glycoprotein (P-gp), but it does appear to have the potential to inhibit the P-gp transport activity.

Additional details related to these overall conclusions are provided in the Investigators Brochure.

5.3 Electrocardiogram (ECG) Assessment

ECG assessments will be performed with standard 12-lead ECG equipment according to standard procedures. Pre-treatment ECGs should be performed at intervals specified in the study calendar, section 10.0.

At any time point, if there is an increase in QTc interval to an absolute value > 500 msec using the Fridericia correction formula, two additional ECGs should be performed approximately 2 minutes apart, within 30 minutes. (See Section 7.1.15: Guidelines for Management of Treatment-Emergent Corrected QT (QTc) Prolongation). Abnormalities in the ECG that lead to a change in subject management (e.g., dose reduced or withheld, requirement for additional medication or monitoring) or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE CRF. If values meet criteria defining them as serious, they must be reported as SAEs.

5.4 Study Treatment Duration

In the absence of treatment delays due to adverse event(s), treatment may continue daily, 7 days per week for four weeks per each treatment cycle.

Subjects may discontinue study treatment or withdraw their consent to participate in the study at any

time without prejudice. The investigator may withdraw a subject from study treatment or from the study if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

In addition, any of the following conditions require discontinuation of the subject from study treatment:

- An AE, unacceptable drug-related toxicity or inter-current illness that in the opinion of the investigator warrants the subject's withdrawal from treatment
- Specific conditions described in the Adverse Events and Risks List, Section 7.1
- The investigator feels it is not in the best interest of the subject to continue on study treatment
- Necessity for treatment with other anticancer treatment prohibited by protocol
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g., male condom, female condom) during the course of the study and for 4 months following discontinuation of study treatment
- Women who become pregnant or are breast feeding
    - If a subject becomes pregnant during the study, she will be taken off study treatment and will be followed through the end of her pregnancy. The investigator must inform the sponsor of the pregnancy. Forms for reporting pregnancies will be provided to the study sites upon request.
    - The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis or designee. Pregnancy, although not itself an SAE, should also be reported on an SAE form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities. Any birth defect or congenital anomaly must be reported as an SAE, and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.
- If the subject does not recover from his or her toxicities to tolerable Grade ≤ 2 within 6 weeks, the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol
- Subject request to discontinue study treatment (with or without concurrent withdrawal of informed consent)
- Significant noncompliance with the protocol schedule in the opinion of the investigator.
- The minimum dose of study treatment will be 20 mg qd. Subjects who cannot tolerate 20 mg qd will have study treatment discontinued.
- Progressive disease (PD) as determined by the investigator.

The reason for study treatment discontinuation will be documented. For subjects who discontinue or

are withdrawn from study treatment, every effort must be made to undertake protocol-specified follow up procedures and end of treatment assessments, if possible, unless consent to participate in the study is also withdrawn.

If a subject fails to return for the protocol-defined visits, an effort must be made to determine the reason. If the subject cannot be reached by telephone, at the minimum a registered letter should be sent to the subject (or the subject's legal guardian) requesting contact with the clinic.

If a subject is discontinued from study treatment because of an AE considered to be related to study treatment and the event is ongoing 30 days after the last dose of study treatment, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible.

Subjects should be instructed to immediately inform the PI of any AEs. Subjects experiencing dizziness, sleepiness, or other symptoms that could influence alertness or coordination should be advised not to drive or operate other heavy machinery.

5.5 Study Post-Treatment and Follow Up

Subjects will return to the study site 30 to 37 days after their last dose of cabozantinib to complete end-of-study assessments. Laboratory and physical examinations will be performed (see Study Calendar section 10.0). Remaining cabozantinib will be returned by the subject, and treatment compliance will be documented. Additional follow-up will occur for subjects with AEs related to study treatment that are ongoing at the time of this visit, and for subjects with SAEs related to study treatment that occur after the time of this visit.

After disease progression, subjects will be followed for survival based upon the timing of the routine clinical care for their disease. Follow-up may occur every 3 months for the first 2 years, then approximately every 6 months x 3 years, then annually. Survival information will be obtained via routine standard of care visits and/or medical record review.

5.6 Duration of Study

Subjects may continue to receive study treatment until they experience unacceptable drug-related toxicity, disease progression or death as defined in Section 5.4. The reason for study removal and the date the patient was removed from study must be documented in the Case Report Form.

If a subject withdraws consent to participate in the study, the reason for withdrawal will be documented, no further study procedures or assessments will be performed, and no further study data will be collected for this subject, other than the determination of survival status from public records such as government vital statistics or obituaries.

Exelixis and/or the Sponsor-Investigator reserve the right to terminate the study, and sub-investigators reserve the right to terminate their participation in the study, at any time. Should this be necessary, Exelixis and the Sponsor-Investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Exelixis and the Sponsor-Investigator

will ensure that adequate consideration is given to the protection of the subjects' interests.

6. DOSING DELAYS/DOSE MODIFICATIONS

Subjects will receive cabozantinib orally at a (starting) dose of 60 mg once daily. Treatment cycles are 4 weeks in duration (28 days).

In all subjects, dose reductions and delays to manage toxicity are allowed under the guidelines in Table 6-1 below. See Section 7, for adverse events list (7.1) and reporting requirements (7.2) associated with dosing delays and/or dose modifications.

Table 6-1: Dose Modification for Cabozantinib	
Dose Level	**Cabozantinib Dose**
0	60 mg daily
-1	40 mg daily
-2	20 mg daily

NOTE*:* *In situations where the toxicity is attributable to cabozantinib requiring a dose reduction beyond dose level -2, cabozantinib will be discontinued, and the patient will be removed from the protocol therapy.*

6.1 Re-escalating study treatment after a dose reduction:

- Subjects who required a dose reduction for a related Grade 3 (unless easily managed) or any Grade 4 non-hematologic adverse event should not be re-escalated
- For other related AEs, subjects may be re-escalated to the previous dose at the discretion of the investigator but not sooner than 2 weeks beyond the resolution to Grade ≤ 1 or to the baseline value of AEs.
- If a subject has been dose-reduced more than once, dose re-escalation can only occur to the next higher dose level. Further dose escalation to higher well-tolerated dose levels is allowed only if clinically indicated per investigator's judgment and dose escalation criteria are met with each escalation (e.g. a minimum 2 week interval between escalations)
- If the AEs that previously led to dose reduction(s) recur at the same grade or higher that previously required a dose reduction, the dose should be reduced again and no further dose escalation will be permitted.
- Dose re-escalation is not allowed for dose reduction triggered by neutropenia or thrombocytopenia.

Additional information for dose delays or dose reductions:

- Dose delays for reason(s) other than AEs related to cabozantinib, such as surgical procedures with no anticancer therapy intent, may be allowed with investigator approval. The acceptable length of interruption will be determined by the investigator.

- Subjects will be instructed to notify their physician immediately of any and all AEs. Subjects experiencing one or more AEs due to the study treatment may require a dosing delay or reduction(s) in their dose in order to continue with study treatment.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting in addition to routine reporting.

Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Seriousness, severity/ grade and relationship to study treatment will be assessed by the investigator. Severity/ grade will be defined by the National Cancer Institute (NCI) CTCAE v4.0. Listings of AEs will be provided.

Subjects will be monitored continuously for AEs throughout the study. **Subjects must be instructed to notify their physician immediately for any and all toxicities**.

Guidelines for the management of AEs (i.e., dose interruptions and dose reductions) are presented in sections 6, Table 6-1. Dose reductions or interruptions are permitted in the setting of lower grade toxicity than defined in the following sections at the discretion of the investigator if the investigator feels it is in the interest of a subject's safety. Each dose reduction of cabozantinib should be to one dose level lower that the current dose. Dose reductions of more than one dose level are acceptable if agreed to by the Investigator. All AEs should also be managed with supportive care at the earliest signs of toxicity considered related to study treatment.

If study treatment of cabozantinib is restarted after being withheld or interrupted, the subject should be instructed not to make up the missed doses of cabozantinib.

The reason for treatment delay and reduced dose must be recorded on the case report form (CRF). Dosing may need to be interrupted for AEs considered not related to cabozantinib if this is clinically indicated or if causality is initially uncertain. Study treatment may be resumed at the same dose (or a lower dose per investigator judgment) if the AE is determined not to be related to cabozantinib once the investigator determines that retreatment is clinically appropriate and the subject meets the protocol re-treatment criteria.

Subjects will be monitored continuously for AEs throughout the study and for 30 days after the last dose of study treatment and for any serious adverse event (SAE) assessed as related to study treatment or study procedures, even if the SAE occurs more than 30 days after the last dose of study treatment.

Abnormalities in clinical laboratory tests that lead to a change in subject management (e.g., dose delayed (withheld) or reduced, requirement for additional medication, treatment or monitoring) are considered clinically significant for the purposes of this study, and will be recorded on the Adverse Events CRF. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE. AE's of grade 2 or greater

or any that result in dose holds or reductions will be collected and reported.

7.1 Adverse Events and Risks List for Cabozantinib

The general adverse event profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea), fatigue, anorexia, weight loss, palmar-plantar erythrodysesthesia (PPE) syndrome, skin rash, elevated ALT and AST, increased pancreatic enzymes with rare cases of pancreatitis, increase in TSH/hypothyroidism as well as side effects associated with inhibition of VEGF signaling such as thrombotic events (e.g., pulmonary embolism [PE] and deep vein thrombosis [DVT]), hypertension, proteinuria, hemorrhagic events, and rare cases of gastrointestinal [GI] perforation, fistula formation and rectal/perirectal abscess. Arterial thromboembolism (transient ischemic attack [TIA], or myocardial infarction [MI]) have been reported rarely. Please refer to the most recent Investigator's Brochure for additional details.

As with all investigational products, unknown AEs may occur. Subjects should be monitored closely throughout their study participation for anticipated AEs related to study treatment(s) additional anticipated AEs potentially related to VEGFR inhibition, as well as unexpected AEs.

The half-life of cabozantinib is 80-172 hours. Thus, when initiating therapy with cabozantinib, it will take most subjects 2-3 weeks to reach steady state. If AEs attributable to cabozantinib occur within the initial 3 week period of dosing, early intervention with dose modifications may be justified for AEs that, if worsened, could potentially be dangerous or debilitating, since without a dose adjustment, systemic exposure of cabozantinib might be expected to increase after the onset of the AE.

7.1.1 General Guidelines for Non-Hematologic and Hematologic Adverse Events

General guidelines for the management of non-hematologic and hematologic toxicities are provided in Table 7-1 and Table 7-2, respectively. As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. Calcium, magnesium, potassium and phosphorus should be kept above the lower limits of the laboratory normal values. For more specific guidelines on gastrointestinal AEs (diarrhea, nausea/vomiting, stomatitis/mucositis), hepatobiliary disorders, pancreatic disorders including lipase and amylase elevations, skin disorders (PPE), embolism and thrombus, hypertension, proteinurea, hemorrhage, rectal and perirectal abscess, gastrointestinal (GI) perforation and GI fistula, non-GI fistula, wound healing and surgery, osteonecrosis of the jaw (ONJ), endocrine disorders and management of treatment-emergent prolongation of the QTc interval, management of fatigue, anorexia, weight loss, eye disorders, musculoskeletal and connective tissue disorders, nervous system disorders, respiratory/thoracic/mediastinal disorders and congenital, familial and genetic disorders refer to Section 7.1.2 – Section 7.1.20 below.

Table 7-1: General Approach to the Management of Cabozantinib-Related Non-Hematologic Adverse Events

CTCAE Version 4 Grade	Guidelines/Intervention
Grade 1:	Add supportive care as indicated. Continue cabozantinib at the current dose level.
Grade 2:	
Grade 2 AEs considered related to cabozantinib that are subjectively tolerable or easily managed	Add supportive care as indicated. Continue cabozantinib at the current dose level.
Grade 2 AEs considered related to cabozantinib that are intolerable to the subject or deemed unacceptable in the investigator's judgment; or are not easily managed or corrected	Dose reduce • If the AE dose not resolve to Grade ≤ 1 or baseline in 7 to 10 days or worsens at any time, cabozantinib dosing should then be interrupted. Then upon resolution to baseline or Grade ≤ 1, the reduced dose should be restarted. • If the AE does resolves to Grade ≤ 1 or baseline without a dose interruption, continue the reduced dose.
Grade 3:	
Grade 3 AEs considered related to cabozantinib which occurred without optimal prophylaxis or which is easily managed by medical intervention or resolved quickly	• Interrupt cabozantinib and add supportive care as indicated • For AEs that are easily managed (e.g., correction of electrolytes) with resolution to baseline or Grade ≤ 1 within 24 hours, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced • For AEs that require supportive care, the dose should be held while supportive care is initiated and optimized. Then upon resolution of the AE to baseline or Grade ≤ 1, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced
Grade 3 AEs considered related to study treatment that occurred despite optimal prophylaxis or is not easily managed by medical intervention	Interrupt study treatment until recovery to ≤ Grade 1 or baseline, and resume treatment with a dose reduction
Grade 4:	
Grade 4 AEs considered related to study treatment	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤ 1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor but only with sponsor approval.

Dose reductions or delays may occur in the setting of lower grade toxicity than defined above if the investigator believes that it is in the interest of the subject's safety.

Table 7-2: General Approach to the Management of Cabozantinib-Related Hematologic Adverse Events

CTCAE Version 4 Grade	Intervention
Neutropenia	
Grade 3 neutropenia with documented infection Grade 3 neutropenia ≥ 5 days Grade 4 neutropenia	Interrupt cabozantinib treatment until resolution to Grade ≤ 1, and resume cabozantinib treatment at a reduced dose.
Thrombocytopenia	
Grade 3 thrombocytopenia with clinically significant bleeding or Grade 4 thrombocytopenia	Interrupt cabozantinib treatment until platelet count is ≥ 100,000/mm^3, and resume cabozantinib treatment at a reduced dose
Febrile Neutropenia	
Grade 3 febrile neutropenia	Interrupt cabozantinib treatment until recovery of ANC to Grade ≤ 1 and temperature to ≤ 38.0°C and resume cabozantinib treatment at a reduced dose.
Grade 4 febrile neutropenia	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤ 1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor but only with sponsor approval.
Other Grade 4 Hematologic Toxicities	
Grade 4 hematologic toxicities other than anemia	Permanently discontinue study treatment unless determined that the subject is clearly deriving clinical benefit. In this case, upon recovery to Grade ≤ 1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor and only with approval by the sponsor.
Grade 4 anemia	Permanent discontinuation for Grade 4 anemia is not mandated. Dose reductions or dose delays for anemia should be applied as clinically indicated. Supportive care such as red blood cell transfusions should be managed according to institutional guidelines.

ANC, absolute neutrophil count; LLN, lower limit of normal

Neutropenia: Grade 1 (LLN ≤ ANC < 1.5 × 10^9/L; Grade 2 (1 × 10^9/L ≤ ANC <1.5 x 10^9/L), Grade 3 (0.5 × 10^9/L ≤ ANC < 1 × 10^9/L), Grade 4 (ANC < 0.5 × 10^9/L).

Febrile Neutropenia: Grade 3 (present); Grade 4 (Life-threatening consequences; urgent intervention indicated).

Thrombocytopenia: Grade 1 (Platelet count <LLN – 75 x 10^9/L); Grade 2 (Platelet count <75.0 – 50.0 x 10^9/L); Grade 3 (Platelet count ≤ 50 - 25 × 10^9/L); Grade 4 (Platelet count < 25 × 10^9/L).

7.1.2 Diarrhea, Nausea, Vomiting, Stomatitis, and Mucositis

Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal agents is recommended at the first sign of diarrhea as initial management. Loperamide is recommended as standard first line therapy. Alternatively, diphenoxylate/atropine can be used. Additional agents to consider in subjects with diarrhea that is refractory to the above include deodorized tincture of opium and octreotide. [45] Some subjects may require concomitant therapy with loperamide, diphenoxylate/atropine, and deodorized tincture of opium to control diarrhea. The dose modification guidance in Table 6-1should be followed. In addition, general supportive measures should be implemented including continuous oral hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals and alcohol.

Nausea and Vomiting

Anti-emetic agents along with supportive care are recommended as clinically appropriate at the first sign of nausea and vomiting. The dose modification guidance in Table 6-1should be followed.
The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure. Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4.

Stomatitis and Mucositis

Preventive measures may include a comprehensive dental examination to identify any potential complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with cabozantinib, good oral hygiene and standard local treatments such as non-traumatic cleansing, and oral rinses (e.g., with a weak solution of salt and baking soda) should be maintained. The oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered

7.1.3 Hepatobiliary Disorders

Elevations of transaminases have also been observed during treatment with cabozantinib. In general, it is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications and alcohol should be discontinued in subjects who develop elevated transaminases.

Since subjects may enter the study with elevations of AST/ALT at baseline, the following guideline should be used for dose modifications:

Transaminase elevation CTCAE v4.0	**Intervention**
Subjects with AST and ALT less than or equal to the ULN at baseline	
Grade 1	Continue cabozantinib with weekly monitoring of liver function tests (LFTs) for at least 4 weeks. Then resume the standard protocol-defined monitoring of LFTs.
Grade 2	Continue cabozantinib with at least twice weekly monitoring of LFTs for 2 weeks. Then weekly for 4 weeks. If LFTs continue to rise within Grade 2, interrupt cabozantinib treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib
Grade 3	Interrupt cabozantinib treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Cabozantinib may then be resumed at a one-dose-level reduction.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose of cabozantinib as determined by the investigator and sponsor but only with sponsor approval.
Subjects with AST or ALT above the ULN but ≤ 3.0 x ULN (i.e., Grade 1) at baseline	
≥ 1.5 fold increase of AST or ALT AND both AST and ALT are ≤ 5.0 x ULN	Continue cabozantinib treatment with at least twice weekly monitoring of LFTs for 4 weeks and weekly for 4 weeks. If LFTs continue to rise, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib
≥ 1.5 fold increase of AST or ALT and at least one of AST or ALT is Grade 3 (i.e. AST or ALT > 5.0 but ≤ 20.0 x ULN)	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator and sponsor but only with sponsor approval.

Cabozantinib treatment should also be interrupted when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (e.g., International Normalized Ratio [INR]). Monitoring of transaminases should be intensified (2–3 times per week) and cabozantinib should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels (INR < 1.5 x ULN, total bilirubin < 1.5 x ULN, aminotransferases ≤ baseline grade).

Subjects must have cabozantinib permanently discontinued if transaminase elevations are accompanied by evidence of impaired hepatic function (bilirubin elevation >2xULN), in the absence

of evidence of biliary obstruction (i.e., significant elevation of alkaline phosphatase) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis), as the combined finding (i.e., Hy's Law cases) represents a signal of a potential for the drug to cause severe liver injury.

All subjects who develop isolated bilirubin elevations of Grade 3 should have study treatment held until recovered to Grade ≤ 1 or baseline (or lower). If this occurs within 6 weeks of the dosing delay, study treatment may continue at a reduced dose. In subjects without biliary obstruction and Grade 4 bilirubin elevation, or with recurrence of Grade 3 bilirubin elevation after a dose reduction, study treatment must be discontinued.

7.1.4 Pancreatic Conditions

Amylase and lipase elevations have been observed in clinical studies with cabozantinib. The clinical significance of asymptomatic elevations of enzymes is not known but in general has not been associated with clinically apparent sequelae. It is recommended that subjects with lipase elevation and/or symptoms of pancreatitis have more frequent laboratory monitoring of lipase and/or amylase (2-3 times per week). Subjects with symptomatic pancreatitis should be treated with standard supportive measures.

Asymptomatic Lipase or Amylase Elevations	
Grade 1 or Grade 2	Continue at current dose level. More frequent monitoring is recommended
Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline, cabozantinib may be restarted at the same dose or at a reduced dose provided that this occurs within 6 weeks. • If retreatment following Grade 3 lipase or amylase elevation is at the same dose and Grade 3 or Grade 4 elevations recur, then treatment must be interrupted again until lipase and amylase levels have resolved to Grade ≤ 1 or baseline and retreatment must be at a reduced dose.
Grade 4	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline and if resolution occurred within 4 days, cabozantinib may be restarted at the same dose or a reduced dose. If resolution took more than 4 days, the dose must be reduced upon retreatment provided that resolution occurred within 6 weeks. • If retreatment following Grade 4 lipase or amylase elevation is at the same dose and Grade 3 or 4 elevations recur, then treatment must be interrupted again until lipase and amylase have resolved to Grade ≤ 1 or baseline and retreatment must be at a reduced dose.

Pancreatitis	
Grade 2 and asymptomatic	• Continue at current dose level. More frequent monitoring of lipase and amylase and radiographic evaluation is recommended.
Grade 2 symptomatic and Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline , cabozantinib may be restarted at a reduced dose if resolution occurred within 6 weeks
Grade 4	Permanently discontinue treatment. However, if the subject was unequivocally deriving benefit from cabozantinib therapy, treatment may resume at a reduced at a reduced dose agreed to by the investigator and sponsor but only with sponsor approval.

7.1.5 Skin Disorders

Palmar-plantar erythrodysesthesia syndrome (PPE; also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported in cabozantinib-treated subjects. All subjects on study should be advised to use prophylactic measures for skin care. These measures includes the use of hypoallergenic moisturizing creams, ointment for dry skin, sunscreen with SPF ≥ 30; avoidance of exposure of hands and feet to hot water; protection of pressure-sensitive areas of hands and feet; and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry. Subjects with skin disorders should be carefully monitored for signs of infection (e.g., abscess, cellulitis, or impetigo).

Early signs of hand-foot syndrome can include tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Aggressive management of symptoms is recommended, including early dermatology referral.

Treatment guidelines for PPE related to study treatment are presented in the table below
In the case of study treatment-related skin changes (e.g., rash, hand-foot syndrome), the investigator may request that additional assessments be conducted with the subject's consent. These assessments may include digital photographs of the skin changes and/or a biopsy of the affected skin and may be repeated until the skin changes resolve.

Hand-Foot Skin Reaction and Hand Foot Syndrome (PPE)	
Grade 1	Continue cabozantinib at current dose. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens.
Grade 2	If tolerable, continue cabozantinib at current dose. If intolerable, reduce cabozantinib dose to next lower level and/or interrupt dosing. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Add analgesics for pain control with NSAIDs/GABA agonists/narcotics if needed. Assess subject at least weekly for changes in severity. If treatment was interrupted (but not reduced), treatment may be restarted at the same dose or at one dose level lower when reaction decreases to Grade 1 or 0. If a treatment interruption is again required, the dose must be reduced when treatment resumes. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time, or affects self-care, proceed to the management guidelines for Grade 3 PPE.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Pain control with NSAIDs/GABA agonists/narcotics. Treatment may restart at one dose level lower when reaction decreases to Grade 1 or 0. Permanently discontinue subject from study if reactions worsen or do not improve within 6 weeks.

GABA, γ-aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drugs; PPE, palmar-plantar erythrodysesthesia

7.1.6 Embolism and Thrombosis

Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the IB). Subjects who develop a PE or DVT should have study treatment held until therapeutic anticoagulation with heparins is established. Study treatment may be resumed with a one dose-level reduction in subjects who have uncomplicated PE or DVT and are deriving clinical benefit from study treatment. During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. Subjects with life-threatening PE or DVT should have study treatment discontinued unless toxicity can be managed and subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor. Venous filters (e.g. vena cava filters) are not recommended due to the high incidence of complications associated with their use. Once a subject is fully anticoagulated, treatment can be restarted per investigator judgment at one dose lower. Subjects should permanently discontinue after a second thrombotic event. Although routine prophylactic anticoagulation is not necessary for all subjects, prophylactic anticoagulation is allowed for individual subjects at the discretion of the investigator. Arterial thrombotic events (e.g., transient ischemic attack, myocardial infarction) have been observed rarely in studies with cabozantinib. Cabozantinib should be discontinued in subjects who develop an acute MI or any other clinically significant arterial thromboembolic complication.

7.1.7 Hypertension

Hypertension is a relatively common complication of other VEGF-pathway inhibitors and has been observed in cabozantinib clinical studies.

Decisions to decrease or hold the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following

the first measurement. Subjects with known hypertension should be optimally managed prior to study entry. Clinical judgment should be used in deciding whether new or worsened hypertension emerging during treatment with cabozantinib requires immediate therapy, or whether therapeutic intervention can be delayed in order to confirm the finding of new or worsened hypertension at a second visit before taking new therapeutic action. It is recommended that this second visit occur within 1 week. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine. Cabozantinib dosing should be interrupted in subjects with severe hypertension (180 mm Hg systolic or 120 mm Hg diastolic; or sustained ≥ 160 mm Hg systolic or ≥ 110 diastolic) who cannot be controlled with medical interventions and discontinued in subjects with hypertensive crises or hypertensive encephalopathy (Table 7-3).

Table 7-3: Management of Hypertension Related to Cabozantinib

Criteria for Dose Modifications	Treatment/cabozantinib Dose Modification
Subjects not receiving optimized anti-hypertensive therapy	
> 140 mm Hg (systolic) and < 160 mm Hg OR > 90 mm Hg (diastolic) and < 110 mm Hg	• Increase antihypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications) • Maintain dose of cabozantinib • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, or if the subject is symptomatic, the dose of cabozantinib should be reduced.
≥ 160 mm Hg (systolic) and < 180 mm Hg OR ≥ 110 mm Hg (diastolic) and < 120 mm Hg	• Reduce cabozantinib by one dose level. • Increase antihypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications) • Monitor subject closely for hypotension. • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced further.
≥ 180 mm Hg (systolic) OR ≥ 120 mm Hg (diastolic)	• Interrupt treatment with cabozantinib Add new or additional anti-hypertensive medications and/or increase dose of existing medications. • Monitor subject closely for hypotension. • When SBP < 140 and DBP < 90, restart cabozantinib treatment at one dose level lower • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced further.
Hypertensive emergency or malignant hypertension	Discontinue all study treatment

BP, blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure

NOTE: If SBP and DBP meet different criteria in table, manage per higher dose-modification criteria

7.1.8 Proteinuria

Proteinuria has been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Proteinuria should be diagnosed and quantified by a UPCR (mg/dL protein / mg/dL creatinine). When a UPCR exceeds 1, a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm the result. Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria > 3.5 grams per day in combination with hypoalbuminemia, edema and hyperlipidemia) or any other relevant renal disease. Also, given the nephrotoxic potential of bisphosphonates, these agents should be used with caution in patients receiving treatment with cabozantinib. Details of management are described in Table 7-4.

Table 7-4: Management of Treatment Emergent Proteinuria

Urine Protein/Creatinine Ratio	Action To Be Taken
≤ 1	• No change in treatment or monitoring
> 1 and < 3.5	• No change in study treatment required • Consider confirming with a 24-hour protein excretion within 7 days • Repeat UPCR within 7 days and once every week. If UPCR is < 1 on two consecutive readings, then UPCR monitoring can revert to protocol specific time points. (The second reading is a confirmatory reading and can be done within 1 week of the first reading.).
≥ 3.5	• Hold cabozantinib immediately and confirm with 24 hour urine protein excretion. • Evaluate for nephrotic syndrome. If present, discontinue cabozantinib treatment permanently, and monitor subject for resolution of nephrotic syndrome. • If proteinuria of ≥ 3.5 g/24 hours is confirmed without diagnosis of nephrotic syndrome, continue to hold cabozantinib and monitor UPCR weekly. If UPCR decreases to < 1.5, restart cabozantinib at a reduced dose. Continue monitoring UPCR once every week until two consecutive readings are < 1, then revert to UPCR monitoring frequency specified in the protocol.

UPCR, urine protein/urine creatinine ratio

7.1.9 Guidelines for the Prevention of Hemorrhagic Events

Hemorrhagic events have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. As preventive measures, subjects should be evaluated for potential bleeding risk factors prior to initiating cabozantinib treatment and monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

- Tumor lesions with cavitations or tumor lesions which invade, encase, or abut major blood vessels. The anatomic location and characteristics of primary tumors or metastases as well as

the medical history should be carefully reviewed in the selection of subjects for treatment with cabozantinib.
- Recent or concurrent radiation to the thoracic cavity
- Active peptic ulcer disease, ulcerative colitis, and other inflammatory GI diseases
- Underlying medical conditions which affect normal hemostasis (e.g., deficiencies in clotting factors and/or platelet function, or thrombocytopenia)
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis
- History of clinically significant hemoptysis

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 0.5 teaspoon (2.5ml) of red blood). Treatment with cabozantinib should be interrupted if less severe forms of clinically significant hemorrhage occur and may be restarted after the cause of hemorrhage has been identified and the risk of bleeding has subsided at a dose agreed to by the sponsor and the investigator. Therapy of bleeding events should include supportive care and standard medical interventions.

Furthermore, subjects who develop tumors abutting, encasing, or invading a major blood vessel or who develop cavitation of their pulmonary tumors while on study treatment must be discontinued from cabozantinib treatment.

7.1.10 Rectal and Perirectal Abscess

Rectal and perirectal abscesses have been reported, sometimes in subjects with concurrent diarrhea. These should be treated with appropriate local care and antibiotic therapy. Cabozantinib should be held until adequate healing has taken place.

7.1.11 Guidelines for Prevention of GI Perforation/Fistula and Non-GI Fistula Formation

GI perforation/fistula and Non-GI fistula formation have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Carefully monitor for episodes of abdominal pain, especially in subjects with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis. Such risk factors include (but may not be limited to) the following:

<u>GI-perforation/fistula:</u>
- Intra-abdominal tumor/metastases invading GI mucosa
- Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess
- Prior GI surgery (particularly when associated with delayed or incomplete healing). Complete healing following abdominal surgery or resolution of intra abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

Additional risk factors include concurrent chronic use of steroid treatment or non-steroidal anti-inflammatory drugs. Constipation indicative of bowel obstruction should be monitored and effectively managed.

Non-GI fistula:

- Radiation therapy has been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with drugs that inhibit VEGF pathways. In addition, subjects who have undergone extensive surgery may be at increased risk of developing a fistula of the involved organs Non GI fistula should be ruled out as appropriate in cases of onset of mucositis after start of therapy.

Discontinue all study treatment in subjects who have been diagnosed with GI or non-GI perforation/fistula.

7.1.12 Wound healing and Surgery

VEGF inhibitors can cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. Therefore, surgical and traumatic wounds must have completely healed prior to starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with cabozantinib.

Treatment with cabozantinib must be interrupted for any wound healing complication which needs medical intervention. Treatment with cabozantinib can be resumed once wound healing has occurred unless otherwise prohibited in specific protocols. Cabozantinib should be discontinued in subjects with serious or chronic wound healing complications.

The appropriate dose hold interval prior to elective surgery to reduce the risk for wound healing complications has not been determined. In general, cabozantinib should be stopped at least 3 weeks (5 half-lives) prior to elective surgery.

7.1.13 Endocrine Disorders

Prospective studies of markers of thyroid functions are currently ongoing in two single-agent studies to characterize the effects of cabozantinib on thyroid function. Preliminary data indicate that cabozantinib affects thyroid function tests (TFTs) in a high number of subjects (See Cabozantinib Investigator's Brochure). Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended for subjects treated with cabozantinib. Management of thyroid dysfunction (e.g., symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

Other endocrine disorders such as hypocalcemia and hyperglycemia, and associated laboratory changes, have been observed in less than 10% of subjects. Monitoring with standard laboratory tests for endocrine disorders and clinical examination prior to initiation and during treatment with cabozantinib is required. Cabozantinib should be discontinued in subjects with severe or life-threatening endocrine dysfunction.

7.1.14 Guidelines for Prevention of Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported with use of antiangiogenic drugs and bisphosphonates and denosumab in cancer patients. Additional risk factors for ONJ have been identified such as use of corticosteroids, chemotherapy, local radiotherapy, poor oral hygiene, smoking, dental or orofacial surgery procedures, and cancer disease itself. Cases of osteonecrosis have been reported in subjects treated with cabozantinib, the details of which are provided in the current version of Investigator's Brochure. As a preventive measure, invasive dental procedures should be avoided if possible in subjects who have previously been treated with or concomitantly receive bisphosphonates or denosumab. In cases where dental procedures are unavoidable, the risks and benefits of a dental procedure and the extent of the procedure as well as the risk of developing osteonecrosis of the jaw need to be considered when deciding on the duration of a temporary treatment interruption of cabozantinib. If clinically possible, treatment with cabozantinib should be held for at least 2 weeks prior to a dental procedure and resumed after complete wound healing occurred.

Subjects with any documented case of osteonecrosis should have study treatment interrupted, and appropriate clinical management should be initiated. Reinitiation of study treatment must be discussed with and approved by the Sponsor on a case by case basis.

7.1.15 Guidelines for Management of Treatment-Emergent Corrected QT (QTc) Prolongation

Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Other factors which may contribute to QTc prolongation include:

- Treatment with other drugs associated with QTc prolongation (see http://www.qtdrugs.org)
- Treatment with CYP3A4 inhibitors (which may increase cabozantinib drug levels)
- Electrolyte changes (hypokalemia, hypocalcemia, hypomagnesemia)
- Medical conditions which can alter electrolyte status e.g., severe or prolonged diarrhea

Subjects having any of these additional risk factors while on cabozantinib must have ECGs performed approximately one week after the onset of these factors.

If at any time on study there is an increase in QTc interval to an absolute value > 500 msec, two additional ECGs should be performed within 30 minutes after the initial ECG with intervals not less than 3 minutes apart. If the average QTcF from the three ECGs is > 500 msec, study treatment must be withheld and the following actions should be taken:

- Check electrolytes, especially potassium, magnesium and calcium. Correct abnormalities as clinically indicated
- If possible, discontinue any QTc-prolonging concomitant medications
- Repeat ECG triplets hourly until the average QTcF is ≤ 500 msec or otherwise determined by

consultation with a cardiologist

The Sponsor should be notified immediately of any QTc prolongation event.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation has resolved. Cardiology consultation is recommended for evaluation and subject management. Symptomatic subjects must be treated according to standard clinical practice. No additional study treatment is to be given to the subject until after the event has resolved, the subject has been thoroughly evaluated, and further treatment has been agreed to by the Sponsor. If any additional study treatment is given (e.g., after correction of electrolyte abnormalities and normalization of QTcF), it will be at a reduced dose as agreed to by the investigator and the Sponsor.

7.1.16 Fatigue, Anorexia and Weight Loss

Fatigue
Common causes of fatigue, such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, sleep disturbance, and hypothyroidism should be ruled out and treated according to standard of care. Pharmacological management should be considered under the direction of the Investigator.

Anorexia and Weight Loss
Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy should be considered for appetite enhancement under the direction of the Investigator.

7.1.17 Musculoskeletal and Connective Tissue Disorders

Cabozantinib appears to represent minimal risk of adverse musculoskeletal effects based on nonclinical GLP-compliant toxicology studies. The development of new or progressive, unexplained musculoskeletal symptoms such as pain or weakness should be assessed for underlying causes.

One event of rhabdomyolysis (CTCAE Grade 4) was reported in a subject with prostate cancer. Cabozantinib should be discontinued in subjects with serious and life-threatening rhabdomyolysis and interrupted if less severe forms occur. Reinitiation of cabozantinib treatment must be discussed with and approved by the sponsor.

7.1.18 Nervous System Disorders

Cabozantinib appears to represent minimal risk of adverse neurological effects based on nonclinical GLP-compliant toxicology studies. Dysphonia, dysgeusia, headache, dizziness, confusional state, convulsion, depression, memory impairment, hypoesthesia, peripheral neuropathy, insomnia, ataxia, and encephalopathy have been observed in clinical studies with cabozantinib. The development of any new or progressive, unexplained neurological symptoms should be assessed for underlying causes.

One confirmed case of RPLS, a syndrome of subcortical vasogenic edema diagnosed by an MRI of

the brain, has been reported in one subject treated with cabozantinib. RPLS should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in patients with RPLS.

7.1.19 Respiratory, Thoracic and Mediastinal Disorders

Dyspnea has been reported in clinical studies with cabozantinib. Symptoms should be managed according to locally accepted clinical practice including an assessment for underlying causes. Pulmonary embolism should be considered as possible causes for new onset dyspnea given the risk of thrombosis associated with inhibition of VEGF signaling. Furthermore, fistula formation (Section 7.1.11) and pneumonia have been reported in subjects treated with cabozantinib and should be considered as clinically indicated in subjects presenting with pulmonary symptoms. Subjects will have frequent clinical evaluations to assess for possible drug-related pulmonary changes.

7.1.20 Genetic Disorders

Cabozantinib was negative in an in vitro bacterial mutagenicity assay, negative in an in vitro chromosomal aberration assay in cultured human peripheral lymphocytes, and negative in an in vivo mouse micronucleus assay.

Safety Definitions

Adverse event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or *life-threatening suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or *serious suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Unexpected adverse event or *unexpected suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

All research subjects will be routinely questioned about adverse events at study visits.

7.1.21 Recording Requirements for Adverse Events

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and; 2) an assessment of the casual relationship between the adverse event and the study drug(s).

AEs or abnormal test findings felt to be associated with the investigational drug or study treatment(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor-Investigator.

7.1.22 Abnormal Test Findings

An abnormal test finding will be classified as an *adverse event* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy.
- Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE.
- The test finding leads to a change in study dosing or discontinuation of subject participation in the clinical study.

- The test finding is considered an AE by the Sponsor-Investigator of the IND application.

7.2 Reporting of Suspected Adverse Reactions

All events meeting the definition of a serious adverse event should be recorded on a MedWatch 3500A Form (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf) or departmental SAE form. Copies should be sent to:

1. Investigator-Sponsor
2. crssafetysubmissions@upmc.edu
3. Local Institutional Review Board per institutional reporting requirements
4. Exelixis, emailed to: drugsafety@exelixis.com or fax to 650-837-7392

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Event Description (section 5) of the MedWatch 3500A form:

- CTCAE term(s) and grade(s)
- Current status of study drug
- All interventions to address the AE (testing and result, treatment and response)
- Hospitalization and/or discharge dates
- Event relationship to study drug

Follow-up reports:
Additional information may be added to a previously submitted report by adding to the original MedWatch 3500A report and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

7.3 Review of Safety Information: Sponsor Responsibilities[1]

The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

7.4 IND safety reports

The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under

[1] 21 CFR Sec. 312.50

Sections 7.5.1 to 7.5.4 below. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

7.4.1 Serious and unexpected suspected adverse reaction

The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

7.4.2 Findings from other studies

The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under section 7.5.1), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

7.4.3 Findings from animal or in vitro testing

The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

7.4.4 Increased rate of occurrence of serious suspected adverse reactions

The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

Submission of IND safety reports

The sponsor must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a FDA Form 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

7.4.4.1 Unexpected fatal or life-threatening suspected adverse reaction reports

The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

7.4.4.2 Reporting format or frequency

FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

7.4.4.3 Investigations of marketed drugs

A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the post marketing safety reporting requirements (e.g., 310.305, 314.80, and 600.80 of this chapter).

7.4.4.4 Reporting study endpoints

Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under paragraph (c) of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under *Serious and unexpected suspected adverse reaction* as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

7.4.5 Follow-up

- The sponsor must promptly investigate all safety information it receives.
- Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report."
- If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under section 7.4 safety reports, is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

7.4.6 Disclaimer

A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

7.5 Reporting adverse events to the responsible IRB

In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the Sponsor-Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) *associated with the investigational drug or study treatment(s)*; 2) *serious*; and 3) *unexpected*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the sponsor-investigator's receipt of the respective information. Adverse events which are 1) *associated with the investigational drug or study treatment(s)*; 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the Sponsor-Investigator's receipt of the respective information.
Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Sponsor-Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1. Additional information can be found in the Investigator's Brochure for Cabozantinib.

8.1 IND Agent Cabozantinib (XL-184)

8.1.1 **Chemical Name:** *N*-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate

Cabozantinib tablets are supplied as film coated tablets containing cabozantinib malate equivalent to 20 mg and 60 mg of cabozantinib and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. All tablet strengths are prepared from a common blend and are distinguished by shape. The 20 mg tablets are round and the 60 mg tablets are oval. The components of the tablets are listed in Table 8-1

Table 8-1: Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w
Cabozantinib malate (25% drug load as cabozantinib)	Active Ingredient	31.7
Microcrystalline Cellulose (Avicel PH-102)	Filler	38.9
Lactose Anhydrous (60M)	Filler	19.4
Hydroxypropyl Cellulose (EXF)	Binder	3.0
Croscarmellose Sodium (Ac-Di-Sol)	Disenegrant	6.0
Colloidal Silicon Dioxide,	Glidant	0.3
Magnesium Stearate	Lubricant	0.75
Opadry Yellow Film Coating which includes: - HPMC 2910 / Hypromellose 6 cp - Titanium dioxide - Triacetin - Iron Oxide Yellow	Film Coating	4.00

8.1.2 Availability

Cabozantinib is an investigational agent supplied to investigators by Exelixis; Exelixis internal number: XL184.

8.1.3 Ordering, Accountability and Compliance

The UPMC CancerCenter Investigational Drug Services (IDS) will maintain accurate records of receipt of all cabozantinib, including dates of receipt, lot number and expiration date, as well as storage criteria in accordance with UPMC CancerCenter IDS policies and procedures defined by the state and federal regulations. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen or error resulting in an overdose, must be recorded and reported even if it does not meet the definition of serious under adverse event reporting.

At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused cabozantinib will be reconciled and destroyed in accordance with applicable state and federal

regulations.

9. BIOMARKER STUDIES

Correlative studies will be performed to identify potential biomarkers of response to cabozantinib, including other known oncogenic drivers in lung adenocarcinoma and HGF co-expression.

Tumor tissue will be mandated at time of study enrollment. All tumors must undergo routine molecular testing (as part of the standard of care) at the UPMC Presbyterian Anatomical and Molecular testing laboratory, which includes Sanger sequencing and SNaPshot analysis for the detection of mutations in the EGFR exons 18-21, KRAS codons 12, 13 and 61, BRAF codon 600 and PIK3CA codons 542, 545 and 1047, in addition to FISH for the EML4-ALK rearrangement, ROS1 rearrangement, c-MET amplification and the KIF5B-RET translocation.

In addition to mandatory archival or tissue from new biopsy at baseline, we will obtain optional research biopsies at time of progression. These samples will allow us to identify both biomarkers for response as well as mechanisms of acquired resistance to cabozantinib. The tissue samples will be used for research purposes (IHC biomarker studies) as well as standard CLIA-certified molecular testing. If a targetable alteration is identified then this may guide post-progression therapy. A core biopsy is preferable, FNA is acceptable, from the most accessible site at which disease progression is evident. In addition to the biomarker assessments listed above for baseline tumor tissue, we will also perform next generation sequencing using the Ion AmpliSeq™ Cancer Panel on Ion Torrent PGM (Life Technologies) (also standard at UPMC). This 50-gene cancer panel includes our standard clinical metastatic lung cancer panel (including KRAS, PIK3CA, BRAF, and EGFR) as well as additional genes of interest (HRAS, AKT1, PTEN, STK11, JAK2/3 and TP53, and CDKN2A).

In patients who do not have an oncogenic driver on routine mutational profiling, the tumors will undergo next generation sequencing using the Ion AmpliSeq™ Cancer Panel on Ion Torrent PGM (Life Technologies) (also standard at the UPMC Presbyterian Anatomical and Molecular testing laboratory). Additional analyses will be performed in tumors and will include c-MET expression, c-MET mutation, and hepatocyte growth factor (HGF) expression.

Serum, plasma, and peripheral blood mononuclear cell (PBMC) samples will be collected at baseline (C1D1) as well on day 1 of cycles 2 and 3 and then at time of progression. Plasma samples for circulating tumor DNA are collected at baseline (C1D1) and time of progression. We hypothesize that markers of increased HGF/MET dependence (MET amplification, MET mutation, high MET expression, high serum HGF and/or sc-MET) at baseline will predict response to cabozantinib and an increase in serum HGF and/or sc-MET after treatment may predict lack of response. We will analyze the predictive value high serum levels of HGF and sc-MET at baseline and during treatment. Baseline and serial HGF and sc-MET as well as other potential biomarker serum levels will be measured using ELISA.

In patients who have paired tumor samples from primary lesions and brain metastases, molecular testing will be performed on both sites of disease, i.e., patients who might have originally presented with early stage or loco-regionally advanced disease and subsequently present with brain metastases will have paired samples available.

The residuals and/or derivatives of samples collected and submitted for studies associated with this protocol will be rendered anonymous and retained at University of Pittsburgh for possible use in future studies. We are collecting peripheral blood mononuclear cells (PBMCs) in anticipation for future analysis of other genetic polymorphisms. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study and destroyed.

Other biomarker studies may be performed as well depending on available funding and available scientific rationale.

10. STUDY CALENDAR

	Within 28 days of 1st Treatment Dose	Within 4 days of 1st Treatment Dose	Day 1 of Cycles 1, 2, and 3	Daily per Treatment Cycle	Day1, Weeks 3,5,7,9,11,13 then every 4 weeks ±5 days	Post-Treatment[12] or Disease Progression
Informed consent	X					
Demographics	X					
Medical and cancer history	X					
Physical exam[1]	X	X			X	X
Vital signs[2]	X	X			X	X
Height	X					
Weight	X	X			X	X
ECOG Performance status	X	X			X	X
CBC w/diff, plts	X	X			X	X
PT/INR, PTT	X	X			X[5]	
Serum chemistry[3,4]	X	X			X	X
TSH, Free T3, Free T4	X	X			X[5]	
Urine Protein/Urine Creatinine ratio (UPCR)	X	X			X	X
Serum Pregnancy test (WOCBP)	X	X			X[5]	X
Research Blood draw			X[6]			X[6]
12-lead Electrocardiogram	X	X			X[5]	X
Tumor Assessment[7]	X[8]				X[9]	X[10]
Concomitant Medications					X	X
Archival Tissue Block[11]	X					
Tumor Tissue Biopsy (Optional)						X[14]
Cabozantinib Administration				X		
Pill count/collection of pill diary					X[13]	
Adverse Event Evaluation	X----------					----------X

1) A physical examination will include assessments of general appearance, skin, HEENT, thorax/lungs, cardiovascular, abdominal, genitourinary, musculoskeletal and neurological findings
2) Vital signs will be conducted at regular intervals and include body temperature, respiratory rate, and blood pressure and pulse. Blood pressure and pulse will be measured after the subject has been sitting for at least 5 minutes
3) Serum Chemistry testing includes: albumin, alkaline phosphatase, ALT, amylase, AST, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, lipase, magnesium, phosphorus,

potassium, sodium, total bilirubin, total protein.

4) Lipase and/or amylase may require more frequent monitoring (2-3 times per week) if a subject has lipase elevation and/or symptoms of pancreatitis
5) Testing to be performed every 4 weeks
6) Serum, plasma, and peripheral blood mononuclear cell (PBMC) samples are collected at baseline (C1D1) and on day 1 of cycles 2 and 3, and then at time of progression. Plasma samples for circulating DNA are collected at baseline (C1D1) and time of progression only.
7) Regular tumor assessments should be performed according to the guidelines in Protocol Section 11 to determine if PD is present
8) Includes assessment of all sites of extra-cranial disease with CT scan, PET-CT and bone scan, as appropriate. MRI brain with contrast (or CT head with contrast in patients who are unable to have an MRI, e.g. has a pacemaker) must be performed within 14 days of the 1st dose of cabozantinib while either not receiving glucocorticoids during the 5 days prior to the baseline brain imaging or on a stable dose of glucocorticoids during the 5 days prior to the baseline brain imaging.
9) All sites of extra-cranial disease must be assessed every 8 weeks. MRI brain (or CT brain with contrast in patients who are unable to have an MRI) must be performed every 8 weeks. In patients whose first site of disease progression is extra-cranial disease, a brain MRI (or CT brain with contrast in patients who are unable to have an MRI) will be performed at the time of extra-cranial disease progression.
10) MRI brain (or CT brain with contrast in patients who are unable to have an MRI) must be performed every 12 weeks in the post-treatment period
11) Archival tissue is mandatory for inclusion to this study. See lab manual for submission instructions.
12) Treatment ends after last scheduled dose of cabozantinib, subject then enters post-treatment period and final testing is performed 30 to 37 days after last treatment dose. After disease progression, subjects will be followed for survival based upon the timing of the routine clinical care for their disease.
13) Starting day 1 of cycle 2 and continuing on day 1 of all subsequent cycles, pills will be counted and the pill diary will be collected to evaluate patient compliance.
14) **Optional**: In addition to tumor tissue for baseline routine molecular testing, additional fresh biopsy of a lesion amenable to safe biopsy from a primary lesion or metastatic site will be requested for molecular biomarker studies at disease progression. Subjects must provide consent to undergo this procedure. See lab manual for submission instructions.

There is a window of ± 1 week available for rescheduling treatment and/or procedures at the discretion of the Sub-investigator, and as discussed with the Investigator if a course is missed or a subject's treatment and/or testing day(s) need to be rescheduled due to the subject's inability to comply with the study calendar (i.e., hospitalizations, business, vacation plans, travel from long distances for study treatment, in advance of the scheduled date to allow ready access to the result(s), reduce financial burden on the subject or reduce travel inconvenience, illness, transportation issues, holidays, family emergencies, etc.).

11. MEASUREMENT OF EFFECT

For this study, computed tomography scans will be performed every 8 weeks for assessment of extra-cranial disease. An MRI of the brain with contrast (or CT brain with contrast in patients who are unable to obtain an MRI, e.g., has a pacemaker) will be performed every 8 weeks to assess intracranial disease.

In patients whose first site of disease progression is extra-cranial disease, a brain MRI (or CT brain with contrast in patients who are unable to obtain an MRI) will be performed at the time of extra-cranial disease progression and every 12 weeks in the study follow-up period.

Subjects continuing to show benefit, (complete response [CR], partial response [PR], or stable disease [SD]) as defined by RECIST v1.1 may continue on study. Subjects with PD as defined by RECIST v1.1 should have their treatment discontinued, and they should enter the post-treatment phase of the study. The same method for tumor assessment should be employed at every assessment.

11.1 Measurability of Tumor at Baseline

At baseline, tumor lesions will be categorized measurable or non-measurable as follows:

11.1.1 Measurable Tumor Lesions

Tumor lesions: must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant Lymph Nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also section below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

11.1.2 Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease; ascites; pleural or pericardial effusion; inflammatory breast disease; lymphangitic involvement of skin or lung; peritoneal spread; abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

11.1.3 Special Consideration Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone Lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can

be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions
- Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment
- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

11.2 Specifications by Methods of Measurements

11.2.1 Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

11.2.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest x-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However,

lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. Still, non-contrast CT is preferred over chest X-ray.

CT and MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

If prior to enrolment it is known that a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) will be used to evaluate the patient at baseline and follow-up, should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer. *For NSCLC and for this study no tumor markers can be used for response assessment.*

Cytology, Histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to

differentiate between response (or stable disease) and progressive disease.

11.3 Tumor Response Evaluation

11.3.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion.

11.3.2 Baseline Documentation of "Target" and "Non-Target" Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means that in instances where patients have only one or two organ sites involved a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions in that organ will be recorded as non-measurable lesions (even if size is greater than 10mm by CT scan).

Target Lesions
Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph Nodes
Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the

measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case report form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

11.4 Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions. Objective response is defined as meeting criteria for either complete response or partial response.

11.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.4.2 Special Consideration on the Assessment of Target Lesions

Lymph nodes:
Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target Lesions that Become 'Too Small to Measure'
While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on

CT scan that the radiologist/physician investigator may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist/physician investigator that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progressions based upon measurement error.

To reiterate, however, if the radiologist/physician investigator is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked. (BML is equivalent to a less than sign <)

Lesions that Split or Coalesce on Treatment
When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

11.4.3 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level (tumor markers are not applicable to assessing response in this study). All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits (tumor markers are not applicable to assessing response in this study).

Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

11.4.4 Special considerations on assessment of progression of non-target disease

When the Patient also has Measurable Disease
In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must

be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient has only Non-Measurable Disease
This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as **'sufficient to require a change in therapy'**. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be **substantial**.

12. DATA REPORTING / REGULATORY REQUIREMENTS

12.1 Data Safety Monitoring Plan

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also

discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPCI DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly by the disease center DSMB.

Both the UPCI DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

12.2 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and Guidelines on Good Clinical Practice compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the Education and Compliance Office – Human Subject Research, Research Conduct and Compliance Office, University of Pittsburgh.

The Investigator (i.e., the study site principal investigator) and the University of Pittsburgh and University of Pittsburgh Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

12.3 Data Handling and Record-Keeping

The Investigator (i.e., the study site principal investigator) will maintain records in accordance with Good Clinical Practice.

The investigator will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational drug; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IND have been discontinued and the FDA so notified.

12.4 Institutional Review Board (IRB) Approval

The investigator (i.e., the study site principal investigator) will obtain, from the University of Pittsburgh Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment, if applicable.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the investigator will promptly notify the University of Pittsburgh IRB of the deviation.

The University of Pittsburgh IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice.

In the event that the University of Pittsburgh IRB requires, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of an sponsor's decision to modify the previously accepted clinical protocol, the sponsor will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of protocol changes requiring the submission of a Protocol Amendment include:

- Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
- Any significant change in the design of the protocol (such as the addition or deletion of a control group).
- The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or AE; or the dropping of a test intended to monitor the safety of the investigational drug.

12.5 Ethical and Scientific Conduct of the Clinical Study

The clinical study will be conducted in accordance with the current IRB-approved clinical protocol; ICH Guidelines on Guidelines on Good Clinical Practice; and relevant policies, requirements, and regulations of the University of Pittsburgh IRB, University of Pittsburgh and University of Pittsburgh Medical Center, Commonwealth of Pennsylvania, and applicable federal agencies.

12.6 Informed Consent

The investigator (i.e., the study site principal investigator) will make certain that an appropriate

informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The investigator, or a sub-investigator(s) designated by the sponsor, will obtain the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The investigator or sub-investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled subjects for continued participation in the clinical study.

12.7 Publication of Data and Protection of Trade Secrets

The Principal Investigator (Protocol Chair) holds the primary responsibility for publication of the study results; provided that the PI will provide any such publication to Exelixis, Inc. for review at least sixty (60) days prior to submission and also comply with any provisions regarding publication as are agreed to between the PI's institution (e.g., institution name.) and Exelixis, Inc. in the Clinical Trial Agreement related to this study. The results will be made public within 24 months of the end of data collection. However, if a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. In any event, a full report of the outcomes should be made public no later than three (3) years after the end of data collection. Authorship for abstracts and manuscripts resulting from this study will be determined according to guidelines established by the International Committee of Medical Journal Editors.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a single institution open-label phase II clinical trial designed to allow a preliminary assessment of the efficacy and safety of cabozantinib in unselected NSCLC patients with metastases to the brain and in the subset of patients with c-MET amplified NSCLC with metastases to the brain.

The hypothesis is that cabozantinib increases ORR from 5% to 15% in patients with NSCLC with brain metastases. The historical ORR in the second–line setting is based on a 5.8% response rate in patients with recurrent NSCLC treated with docetaxel.[14] In a prior study of patients with metastatic NSCLC, the 12-week ORR for cabozantinib was 10% (95% confidence interval 5%-20%).[8] Based on our preliminary data, we anticipate a higher ORR in patients with brain metastases.

Therefore, target enrollment is 54 evaluable patients (defined below). Simon's optimal two-stage design is used to minimize the expected sample size if the treatment is not effective. A stopping rule for futility is implemented if 1 or fewer of the first 29 evaluable patients have an objective response. (Accrual may continue during follow-up for these patients.) If ≥2 responses are observed in the first 29 evaluable patients, an additional 25 patients will be enrolled. A promising study result would be a response rate of 6/54 (11%) or greater. This design has 82% power to detect a true response rate of 15% (compared with a null rate of 5%). A minimum of 15 evaluable patients with *c-MET* amplified tumors will be enrolled. If 1 or fewer than 29 patients in the first stage of the Simon design have an objective response and fewer than 15 of the 29 have *c-MET* amplified tumors, accrual will continue for the *c-MET* amplified patients only to reach a minimum of 15 evaluable patients with *c-MET* amplification.

The ORR will be reported for the unselected population (all evaluable patients) and for patients with *c-MET* amplification. A 90% and 95% Wilson confidence interval for the ORR will also be reported. With a minimum of 15 patients with *c-MET* amplification, a promising ORR should be detectable. For example, the 95% Wilson confidence interval for a 3/15 ORR (20%) is (7%, 45%).

13.2 Sample Size/Accrual Rate

Approximately 54 subjects will be enrolled in the study. A minimum of 15 patients with *c-MET* amplified tumors is required. Accrual rate and completion through last study follow-up visit is estimated at 3 years.

13.3 Study and Safety Populations

The efficacy population will consist of all subjects who receive any amount of study treatment and are evaluable for response. Response will follow RECIST 1.1 criteria (Appendix B) when at least one follow-up scan has been performed. A subject who withdraws from the study before a follow-up scan for disease progression will may be counted as evaluable without an objective response or omitted from analysis (not evaluable):

- No follow-up scans for RECIST 1.1, no objective response (evaluable):
- Progressive disease
- Withdraw due to treatment toxicity
- No follow-up scans for RECIST 1.1, omit from analysis (not evaluable)
- Withdraw consent for reasons other than progressive disease or toxicity
- Belatedly discovered to be ineligible for enrollment

13.4 Safety Analysis

All safety analyses will be performed using the safety population.

Adverse events will be graded using the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events version 4.0. Adverse events of grade 2 or greater, or that

result in dose holds or reductions, will be collected and reported. The number and percent of subjects reporting adverse events will be summarized by category (i.e., "Blood and lymphatic system disorders"), for the most common adverse event subcategories (i.e., "anemia"), and for serious adverse events (defined in section 7.2). Narratives of all serious adverse events and deaths on-study will be provided.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: EVALUATION OF LESIONS USING RECIST 1.1 CRITERIA

Evaluation of Target Lesions using RECIST 1.1 Criteria

Complete response (CR): Disappearance of all target lesions. Any pathological lymph node (LN) target or no must have decreased in short axis to <10mm.

Partial response (PR): At least a 30% decrease in the sum of the LD of the target lesions taking as reference the baseline sum LD.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of the target lesions taking as reference the smallest sum LD recorded since the treatment started including baseline if that is the smallest on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions also constitutes PD.

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

Evaluation of Non-Target Lesions using RECIST 1.1 Criteria

Complete response (CR): Disappearance of all non-target lesions and normalization of tumor marker levels. All LN must be non-pathological in size (<10mm short axis).
Non-complete response (non-CR)/non-progression (non-PD): Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of Response at each Time-Point using RECIST 1.1 Criteria

Target lesions	Non Target lesion	New lesion	Overall response
CR	CR	No	CR
CR	Non-CR/Non PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response; PR=partial response; SD=stable disease; and PD=progressive disease.

Evaluation of Best Overall Response using RECIST 1.1 Criteria

The best overall response is defined as the best response achieved across all time points prior to

progression (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). See Eisenhauer EA, Therasse P, Bogaerts J, et al. Eur Cancer.2009;22:228-248 for full publication of RECIST 1.1.

Other Efficacy Parameters
PFS is defined as the time from the start of treatment until documented disease progression as defined via RECIST 1.1 or death. Overall survival is defined as the time from the start of treatment until death due to any cause.